FIG. 1

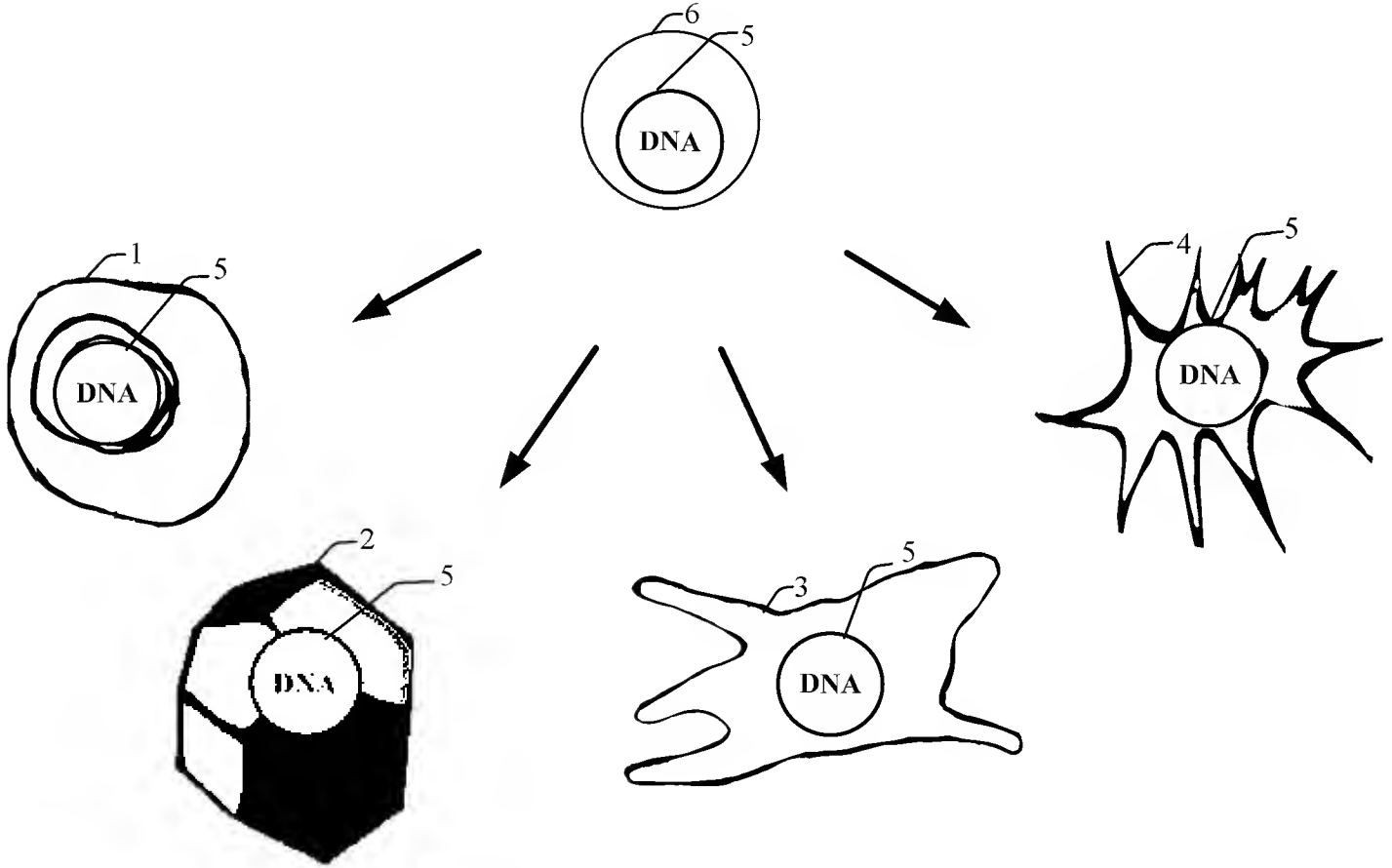


FIG. 2A

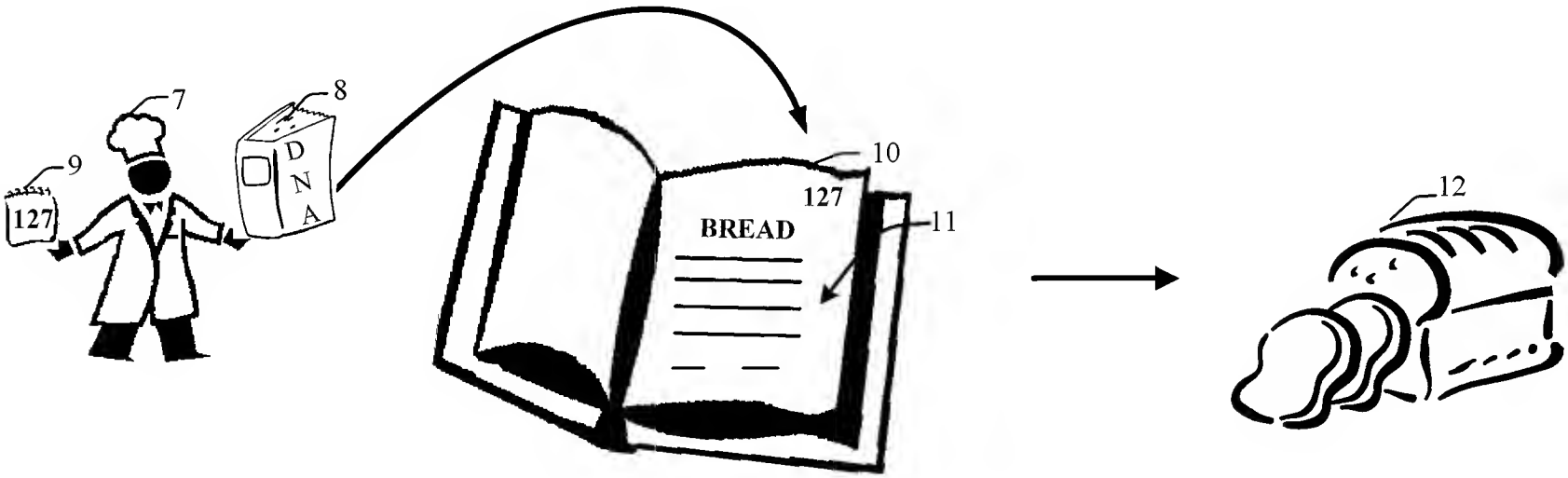


FIG. 2B

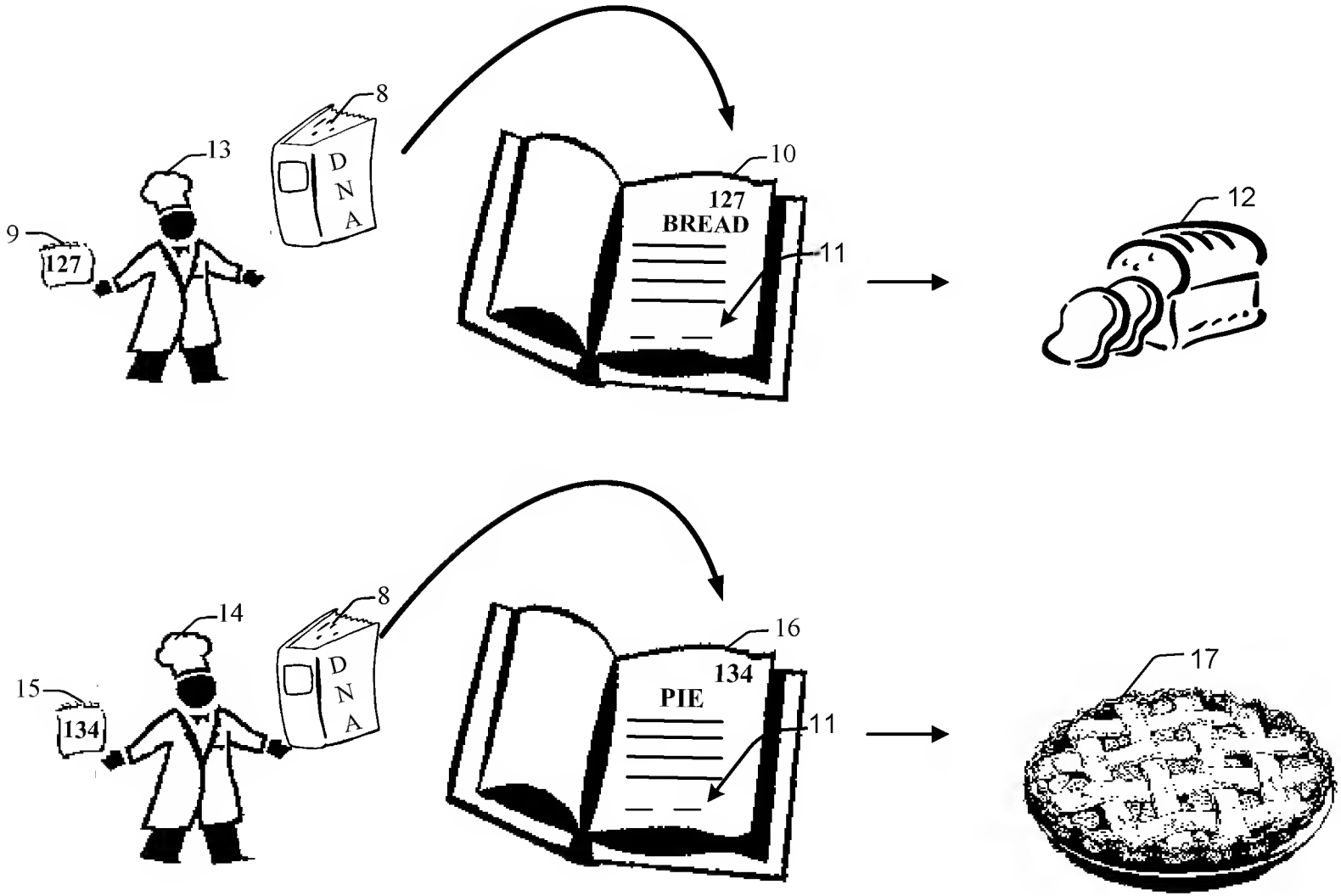


FIG. 3

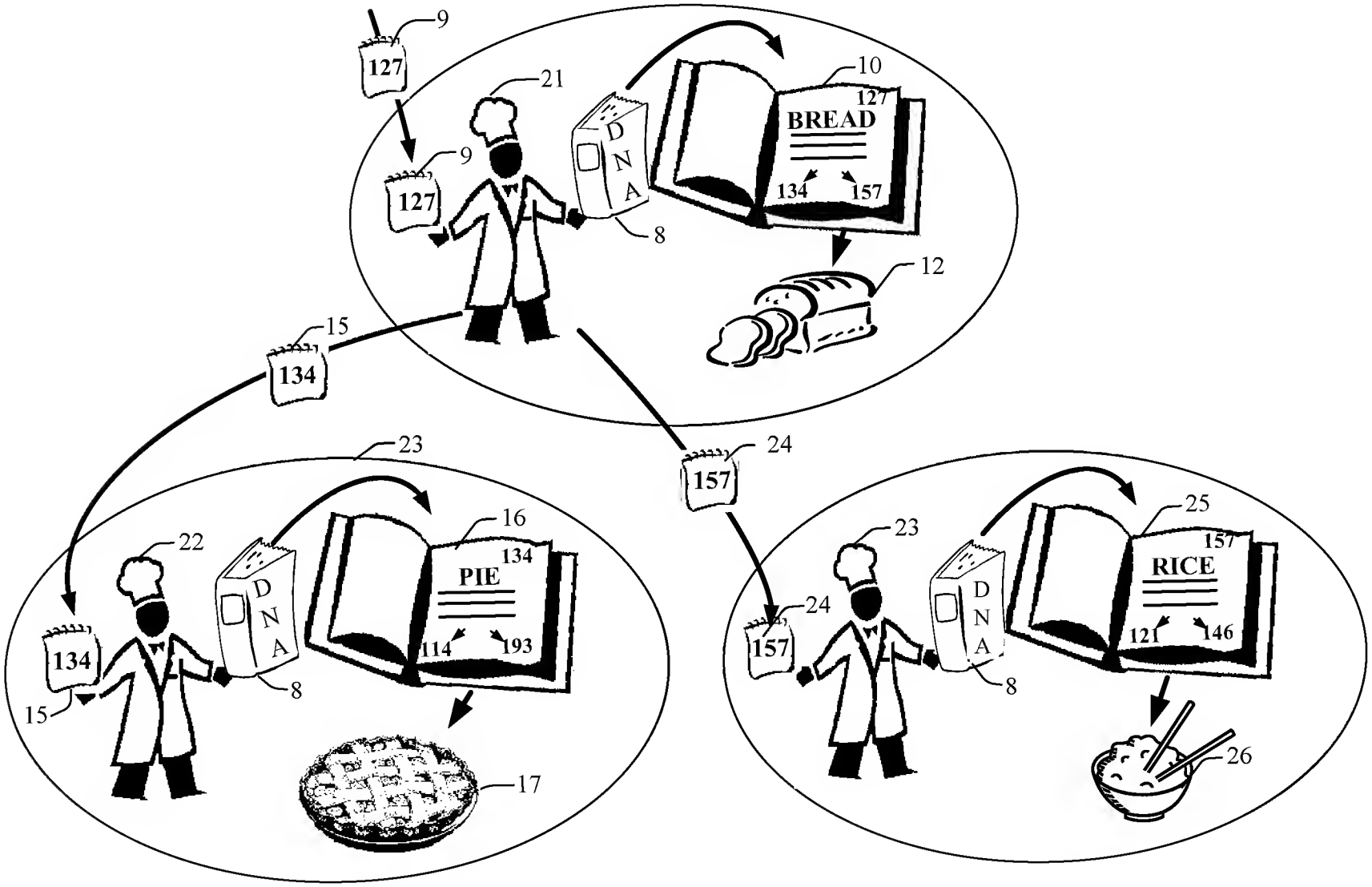

9
127
21
10
127
BREAD
134
157
D
N
A
8
12
15
134
23
24
157
22
16
134
PIE
114
193
25
157
RICE
121
146
23
24
157
8
15
17
26

FIG. 4

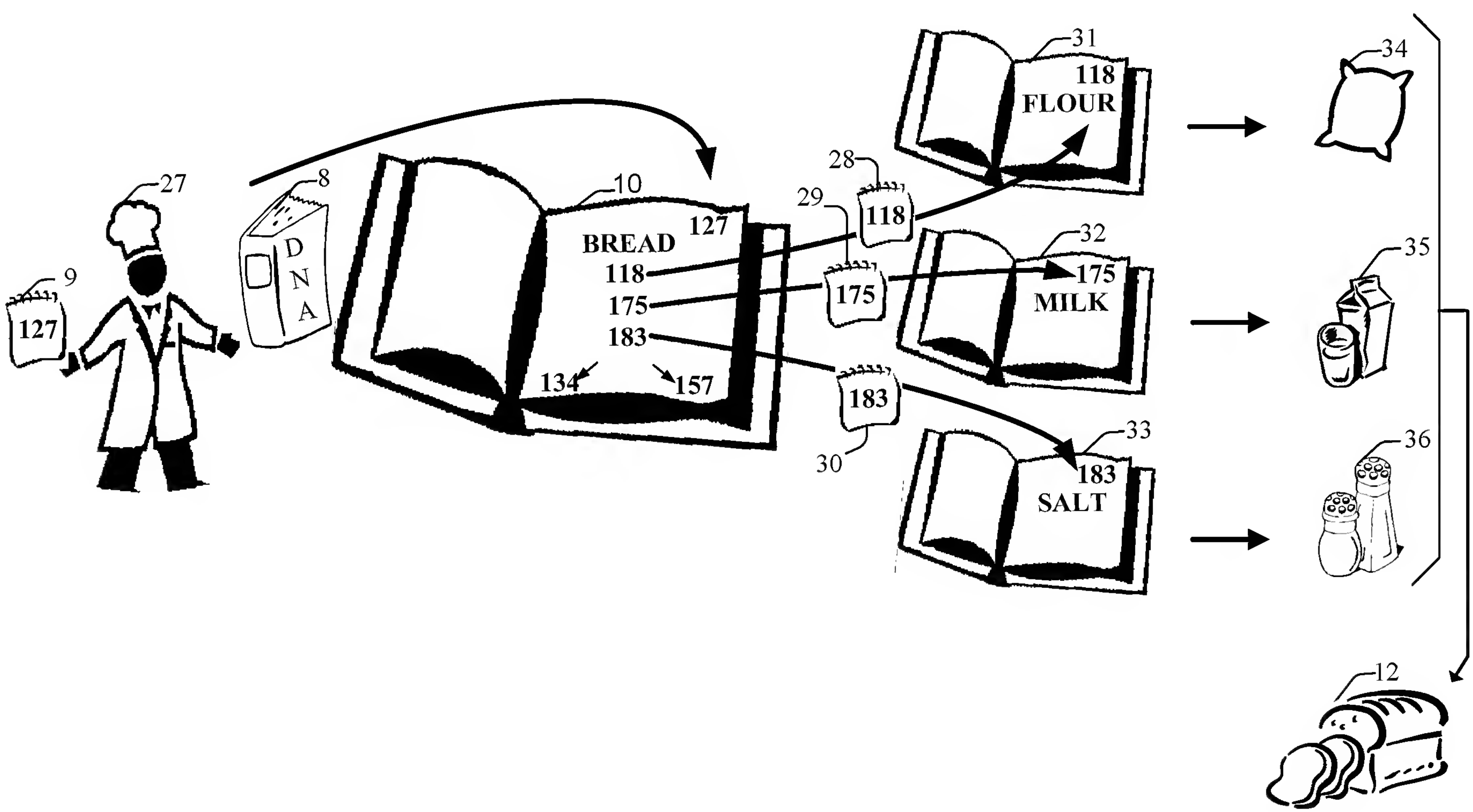

127
9
27
D
N
A
8
10
BREAD
127
118
175
183
134
157
28
118
29
175
183
30
31
118
FLOUR
32
175
MILK
33
183
SALT
34
35
36
12

FIG. 5A

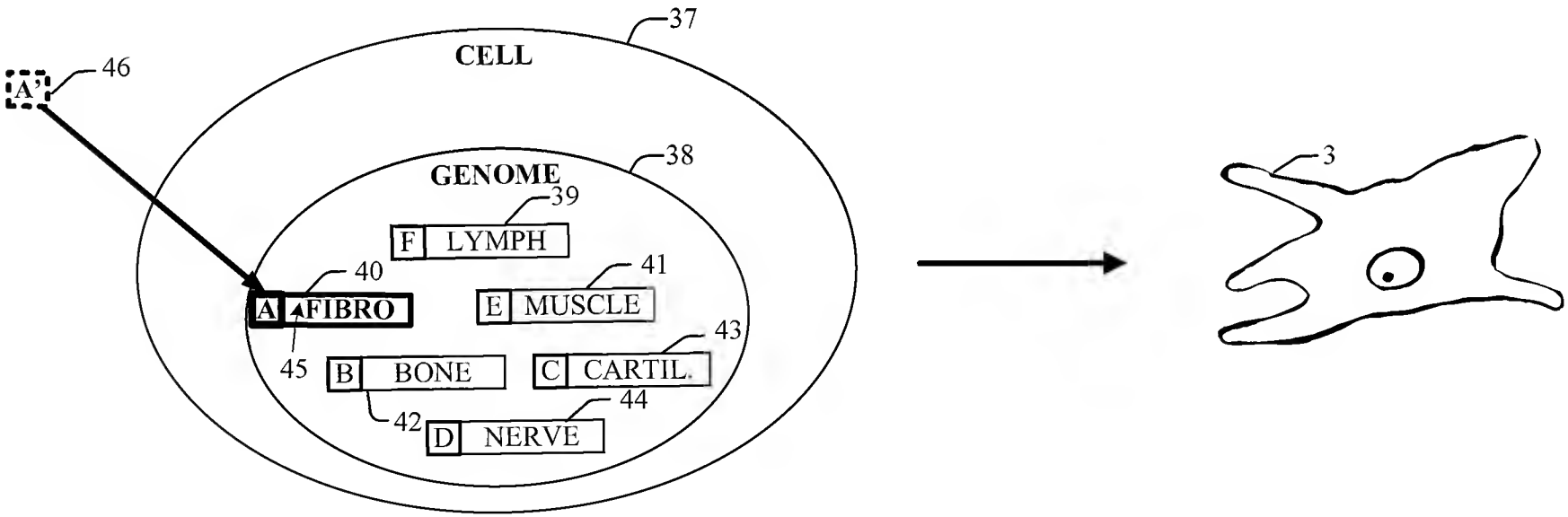

A'
46
CELL
37
GENOME
38
39
F LYMPH
40
41
A FIBRO
E MUSCLE
45
43
B BONE
C CARTIL.
42
44
D NERVE
3

FIG. 5B

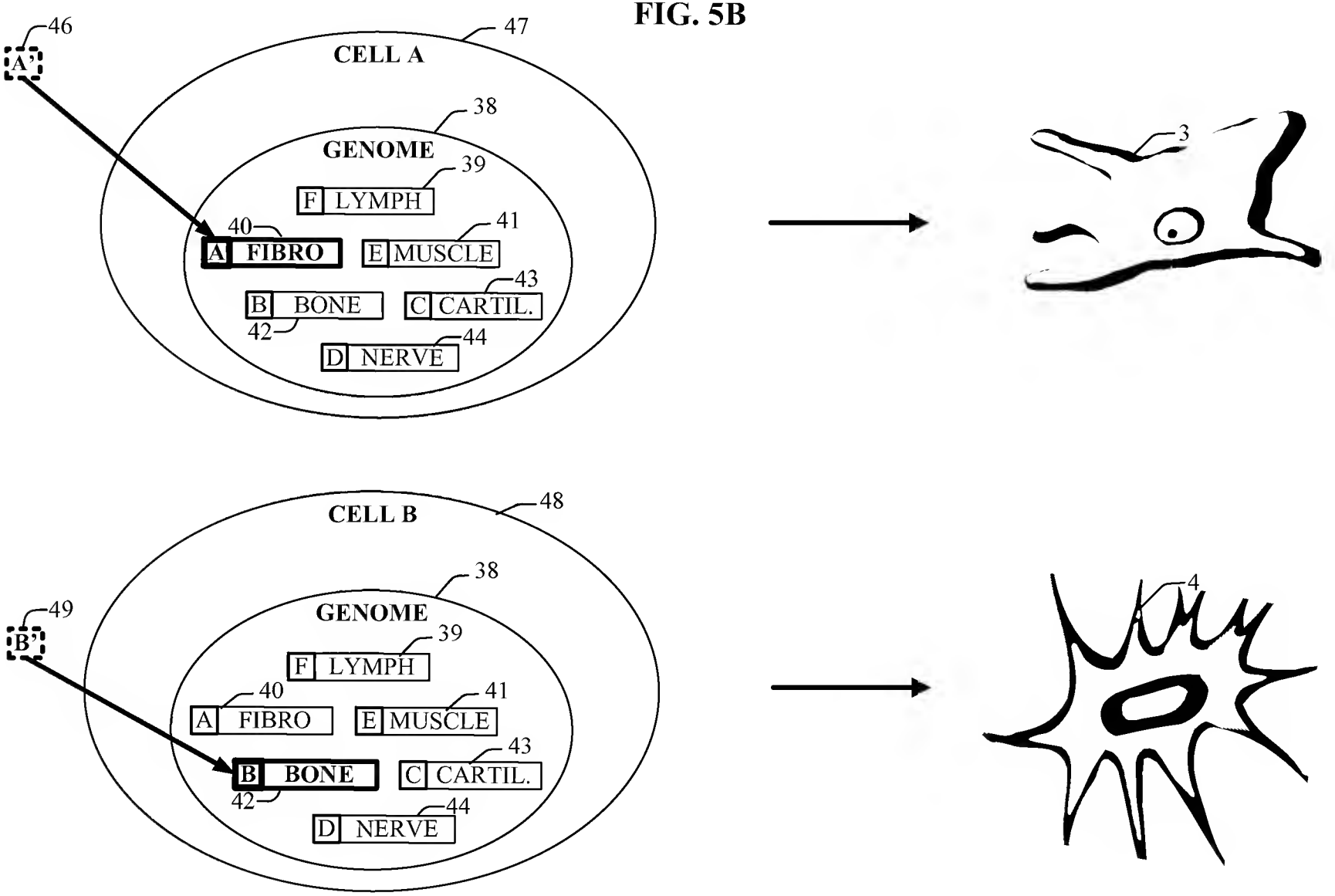

46
A'
47
CELL A
38
GENOME
39
F LYMPH
40
A FIBRO
41
E MUSCLE
43
B BONE
C CARTIL.
42
44
D NERVE
3
48
CELL B
38
GENOME
49
B'
39
F LYMPH
40
A FIBRO
41
E MUSCLE
43
B BONE
C CARTIL.
42
44
D NERVE
4

FIG. 6

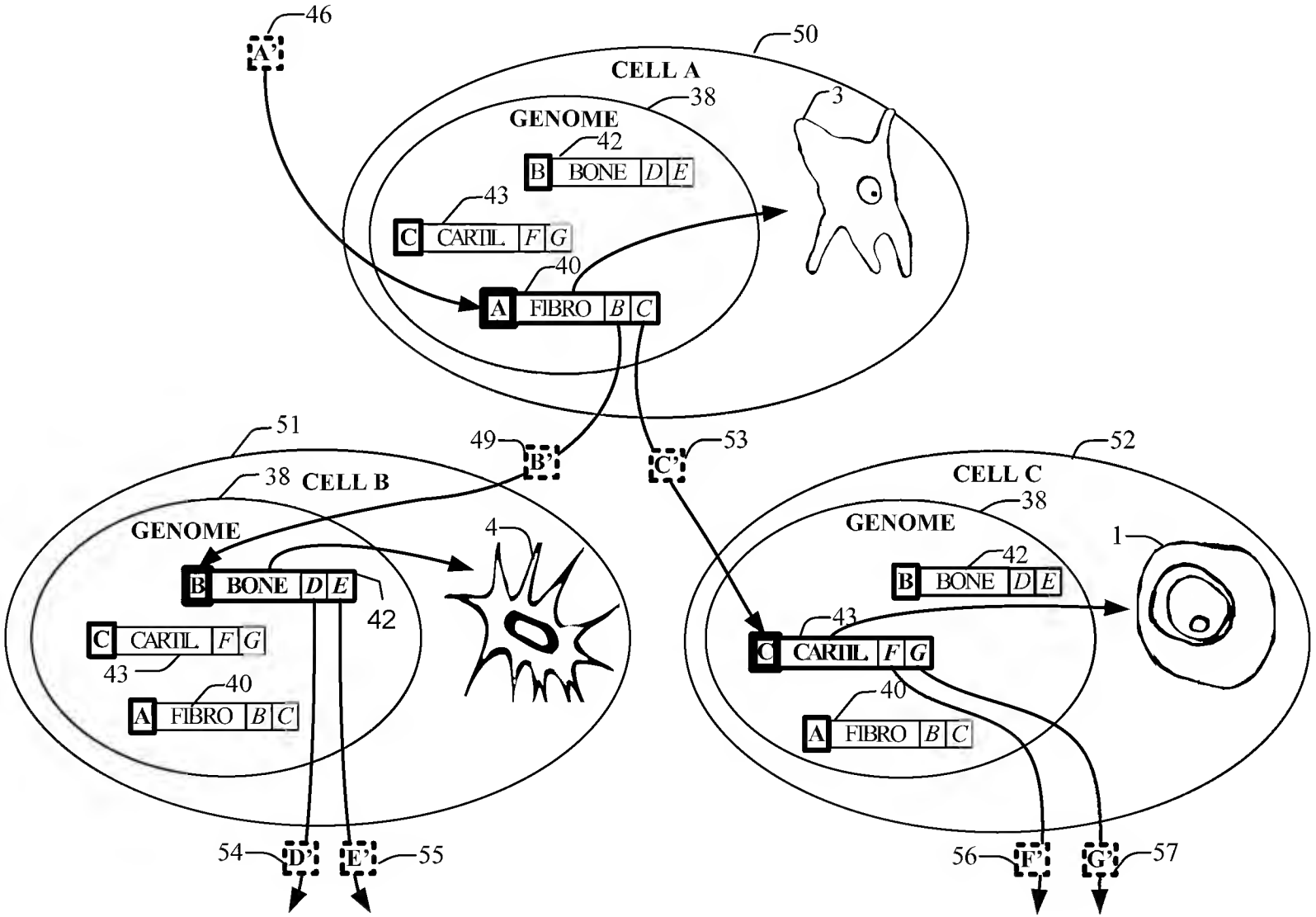

46
A'
50
CELL A
38
GENOME
3
42
B BONE D E
43
C CARTIL. F G
40
A FIBRO B C
49
B'
C'
53
51
38 CELL B
GENOME
4
B BONE D E
42
C CARTIL. F G
43
40
A FIBRO B C
52
CELL C
38
GENOME
1
42
B BONE D E
43
C CARTIL. F G
40
A FIBRO B C
54
D'
E'
55
56
F'
G'
57

FIG. 7

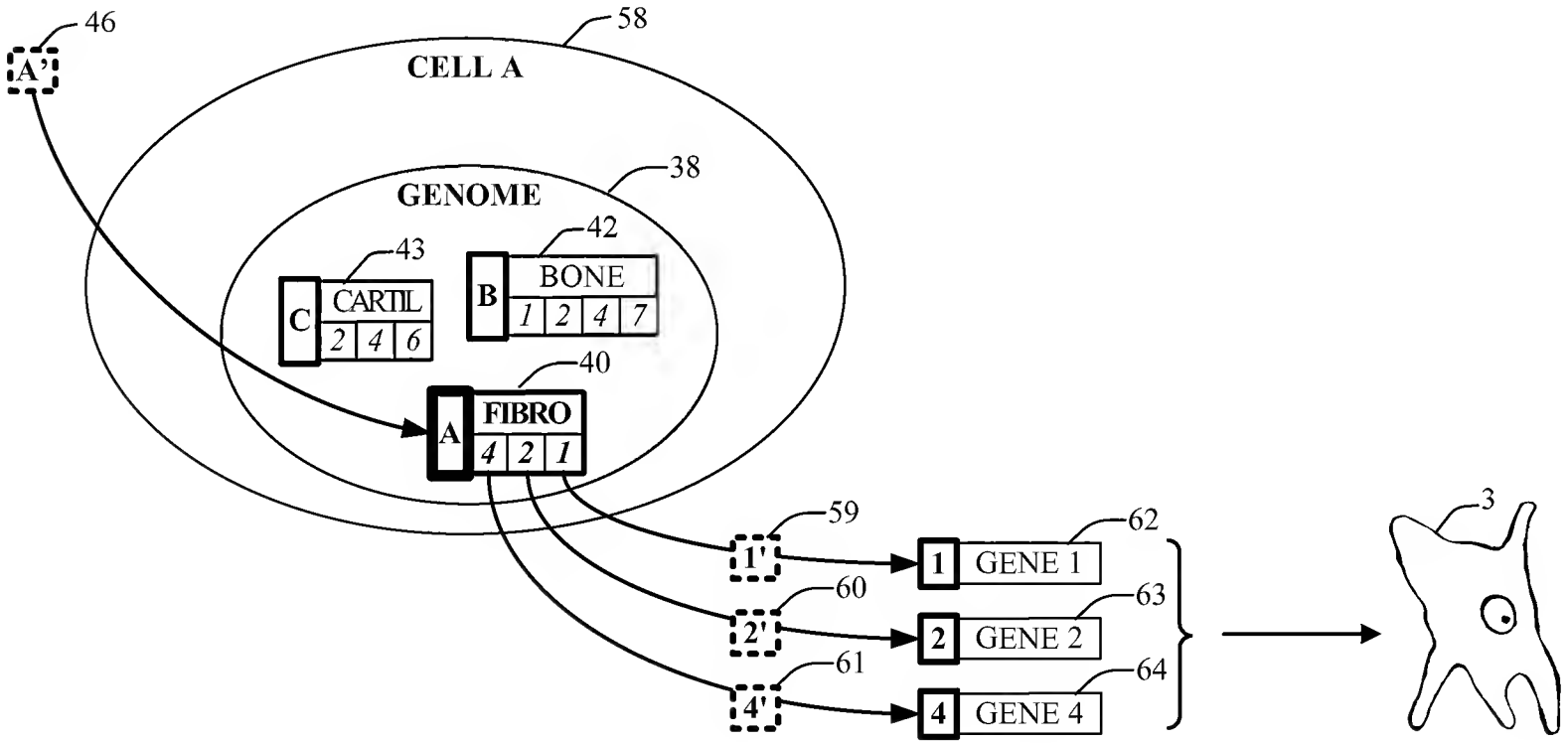

46
A'
58
CELL A
38
GENOME
43
C
CARTIL
2 4 6
42
B
BONE
1 2 4 7
40
A
FIBRO
4 2 1
59
1'
60
2'
61
4'
62
1
GENE 1
63
2
GENE 2
64
4
GENE 4
3

FIG. 8

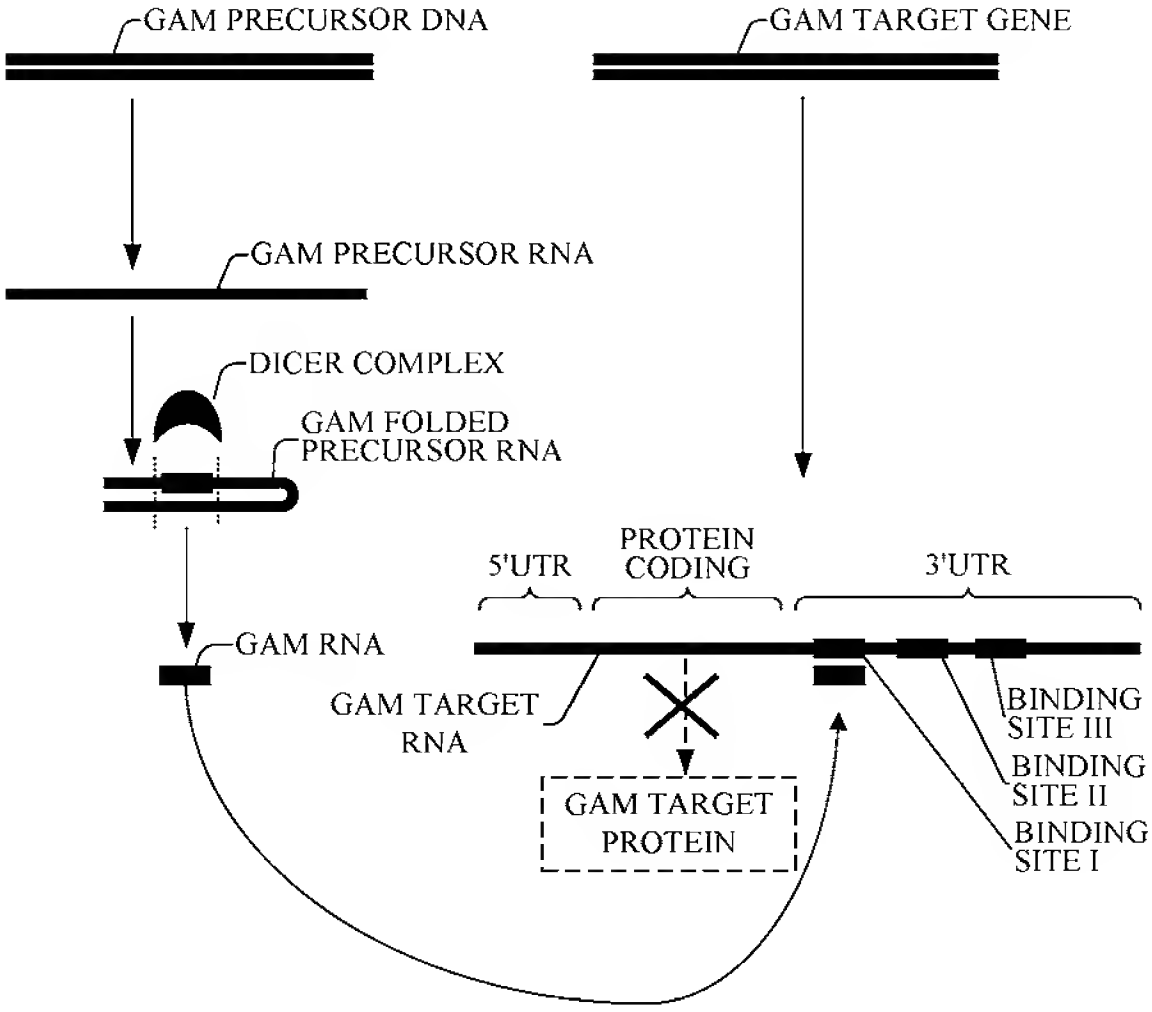

GAM PRECURSOR DNA
GAM TARGET GENE
GAM PRECURSOR RNA
DICER COMPLEX
GAM FOLDED
PRECURSOR RNA
5'UTR
PROTEIN
CODING
3'UTR
GAM RNA
GAM TARGET
RNA
BINDING
SITE III
BINDING
SITE II
BINDING
SITE I
GAM TARGET
PROTEIN

FIG. 9

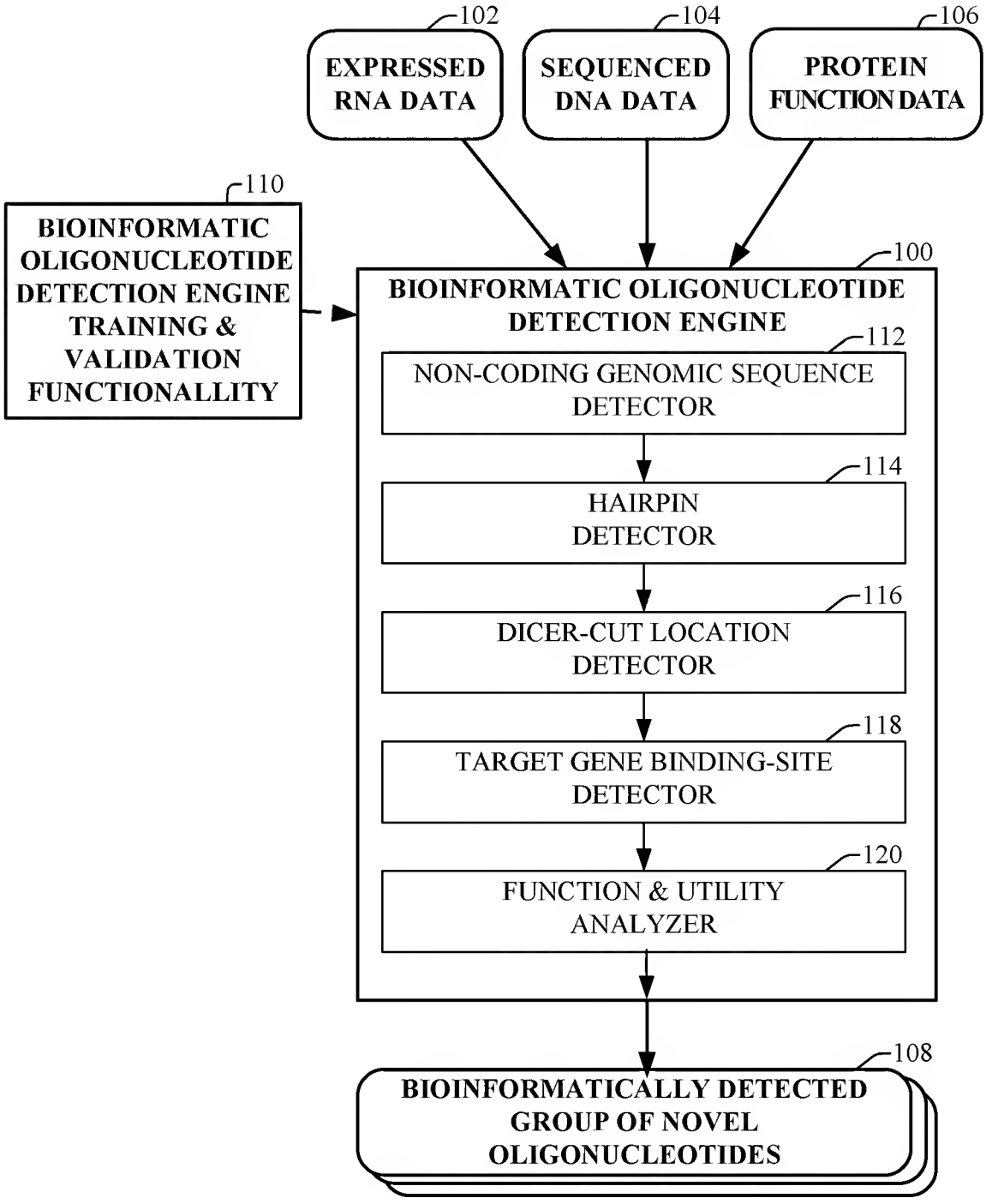

102
EXPRESSED RNA DATA
104
SEQUENCED DNA DATA
106
PROTEIN FUNCTION DATA
110
BIOINFORMATIC OLIGONUCLEOTIDE DETECTION ENGINE TRAINING & VALIDATION FUNCTIONALLITY
100
BIOINFORMATIC OLIGONUCLEOTIDE DETECTION ENGINE
112
NON-CODING GENOMIC SEQUENCE DETECTOR
114
HAIRPIN DETECTOR
116
DICER-CUT LOCATION DETECTOR
118
TARGET GENE BINDING-SITE DETECTOR
120
FUNCTION & UTILITY ANALYZER
108
BIOINFORMATICALLY DETECTED GROUP OF NOVEL OLIGONUCLEOTIDES

FIG. 10

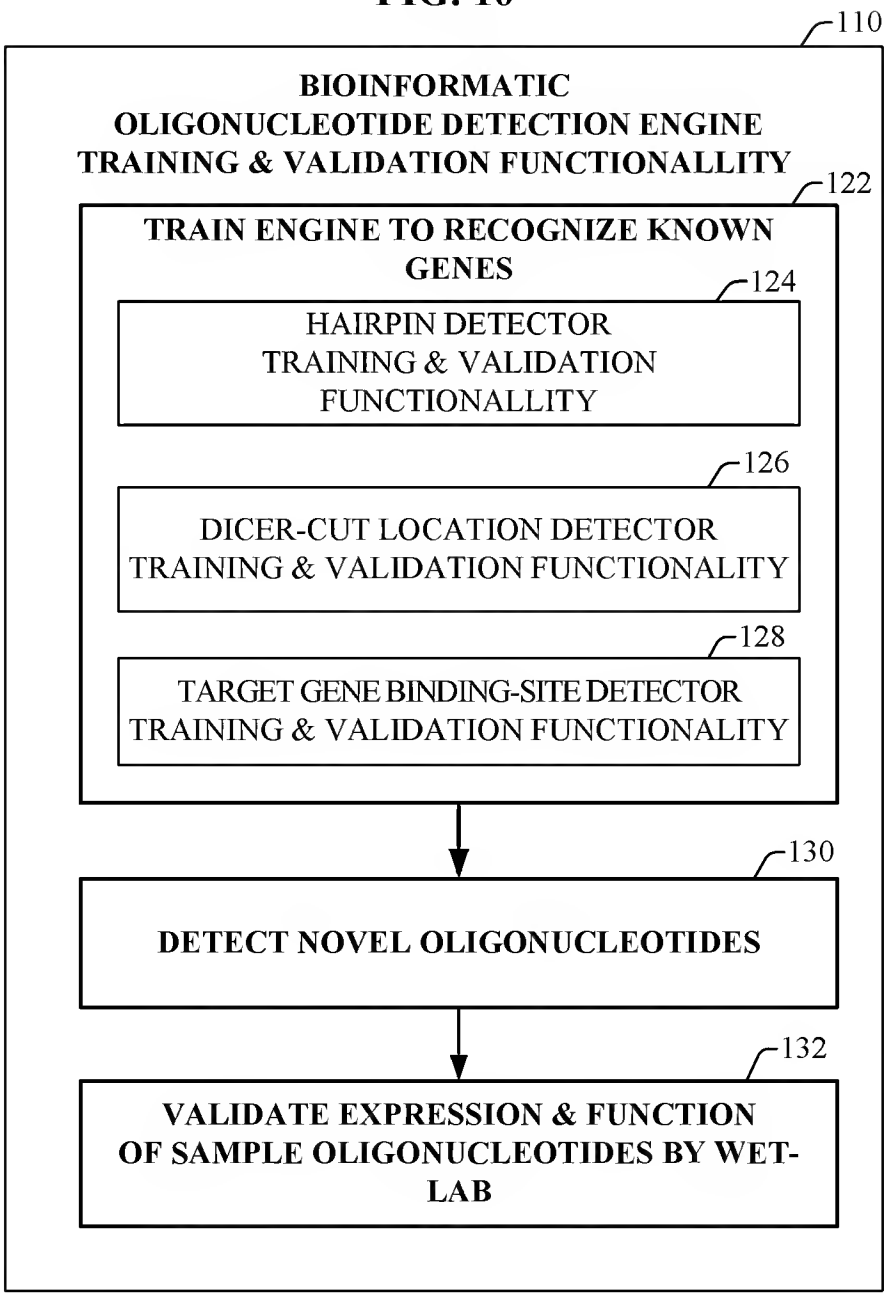

110
BIOINFORMATIC OLIGONUCLEOTIDE DETECTION ENGINE TRAINING & VALIDATION FUNCTIONALLITY
122
TRAIN ENGINE TO RECOGNIZE KNOWN GENES
124
HAIRPIN DETECTOR TRAINING & VALIDATION FUNCTIONALLITY
126
DICER-CUT LOCATION DETECTOR TRAINING & VALIDATION FUNCTIONALITY
128
TARGET GENE BINDING-SITE DETECTOR TRAINING & VALIDATION FUNCTIONALITY
130
DETECT NOVEL OLIGONUCLEOTIDES
132
VALIDATE EXPRESSION & FUNCTION OF SAMPLE OLIGONUCLEOTIDES BY WET-LAB

FIG. 11A

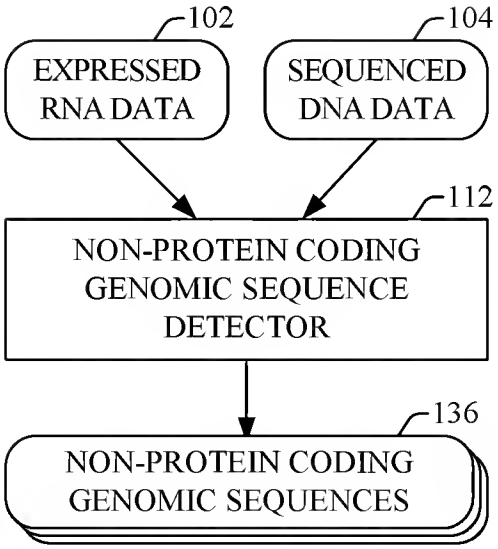


FIG. 11B

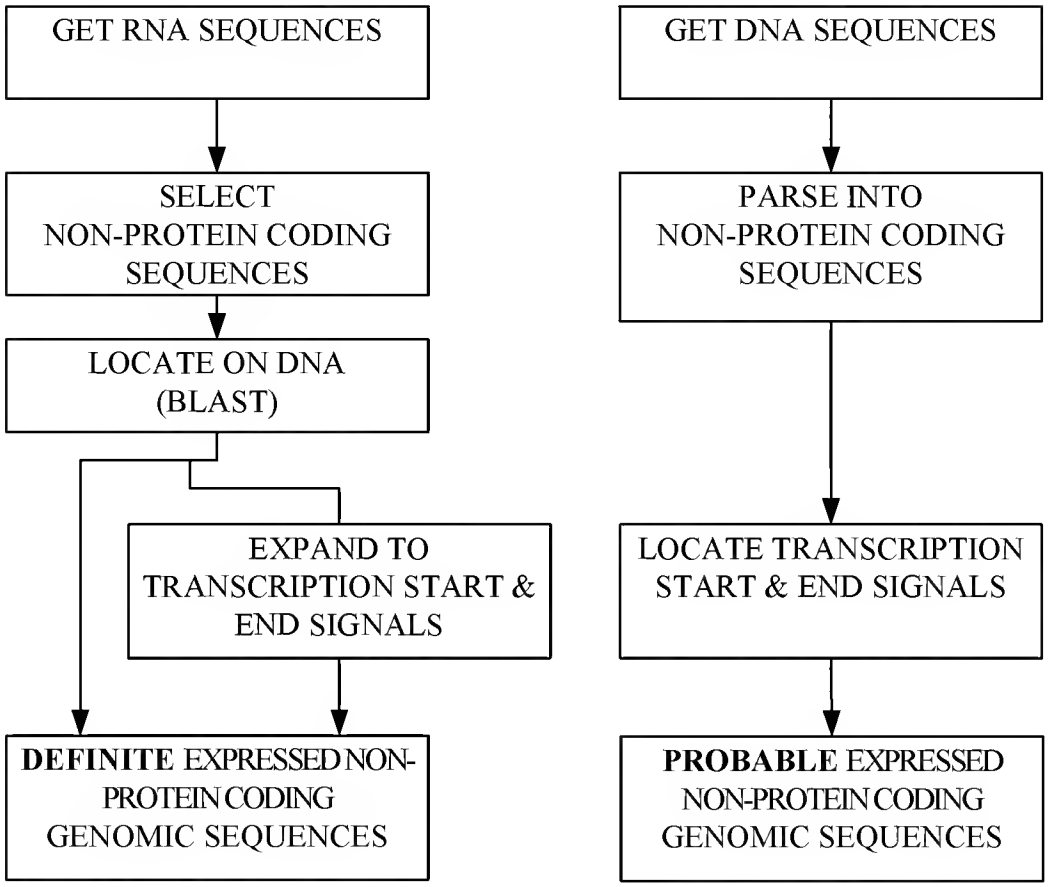


FIG. 12A

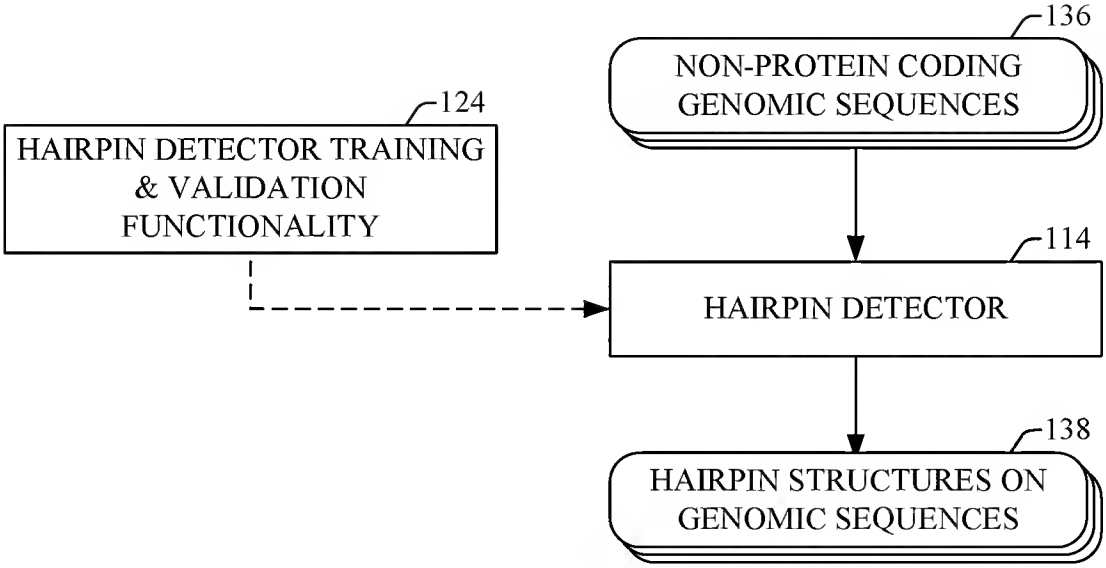


FIG. 12B

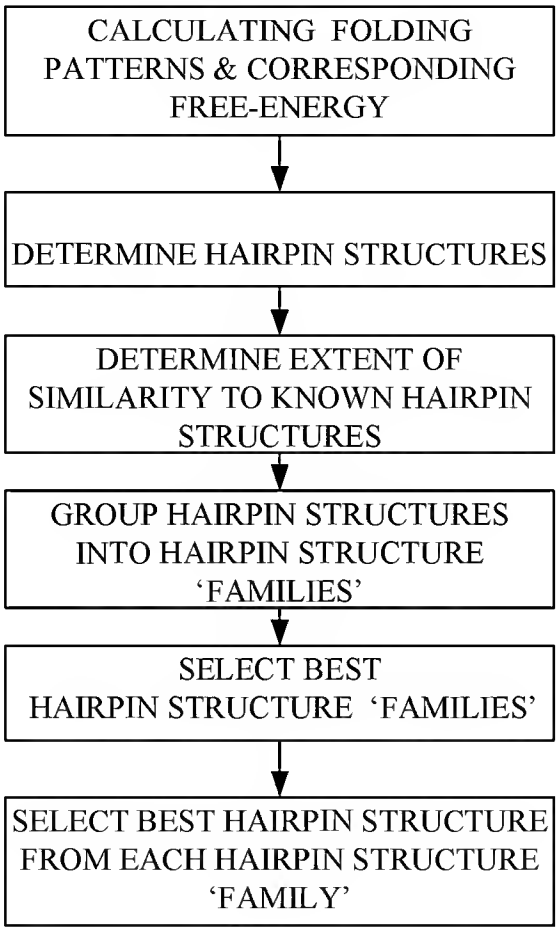


FIG. 13A

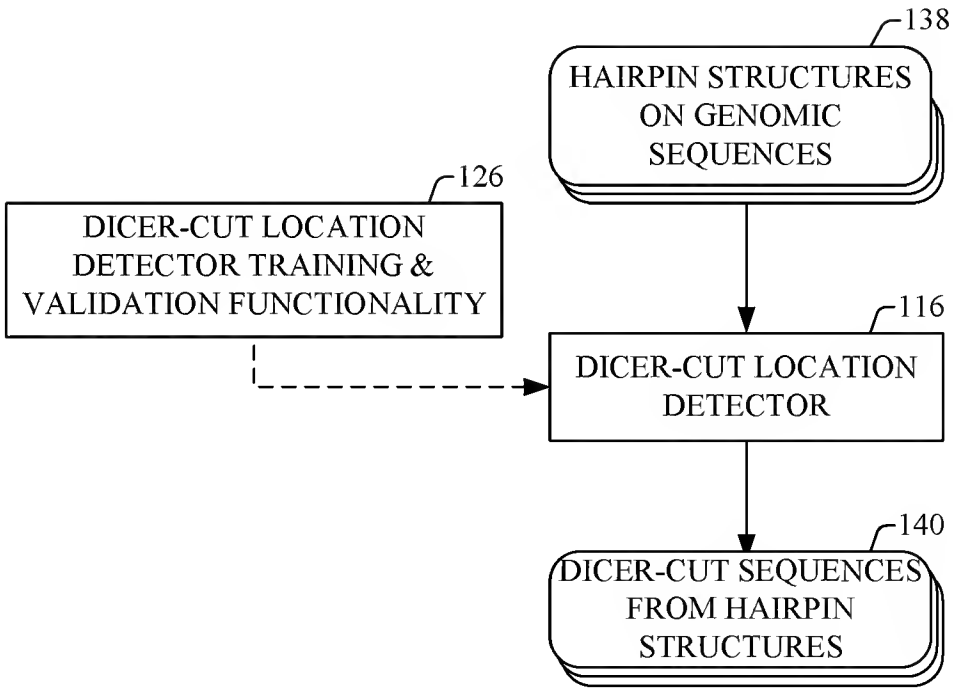

138
HAIRPIN STRUCTURES ON GENOMIC SEQUENCES
126
DICER-CUT LOCATION DETECTOR TRAINING & VALIDATION FUNCTIONALITY
116
DICER-CUT LOCATION DETECTOR
140
DICER-CUT SEQUENCES FROM HAIRPIN STRUCTURES

FIG. 13B

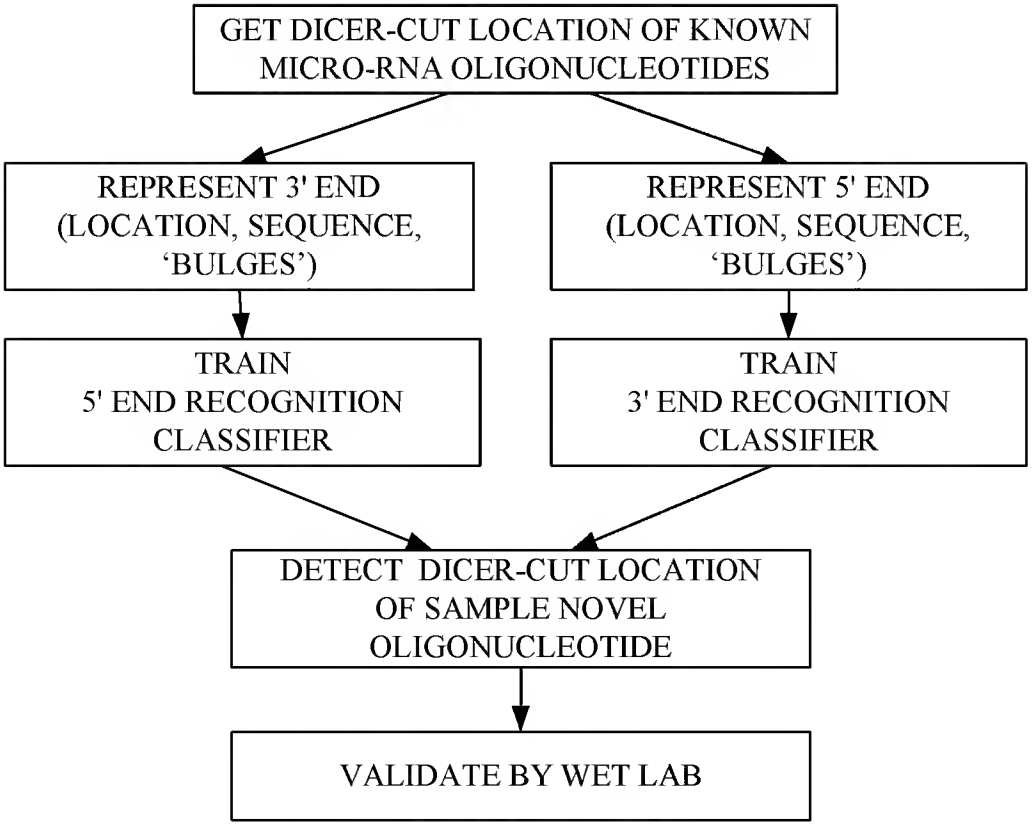

GET DICER-CUT LOCATION OF KNOWN MICRO-RNA OLIGONUCLEOTIDES
REPRESENT 3' END (LOCATION, SEQUENCE, 'BULGES')
REPRESENT 5' END (LOCATION, SEQUENCE, 'BULGES')
TRAIN 5' END RECOGNITION CLASSIFIER
TRAIN 3' END RECOGNITION CLASSIFIER
DETECT DICER-CUT LOCATION OF SAMPLE NOVEL OLIGONUCLEOTIDE
VALIDATE BY WET LAB

FIG. 13C

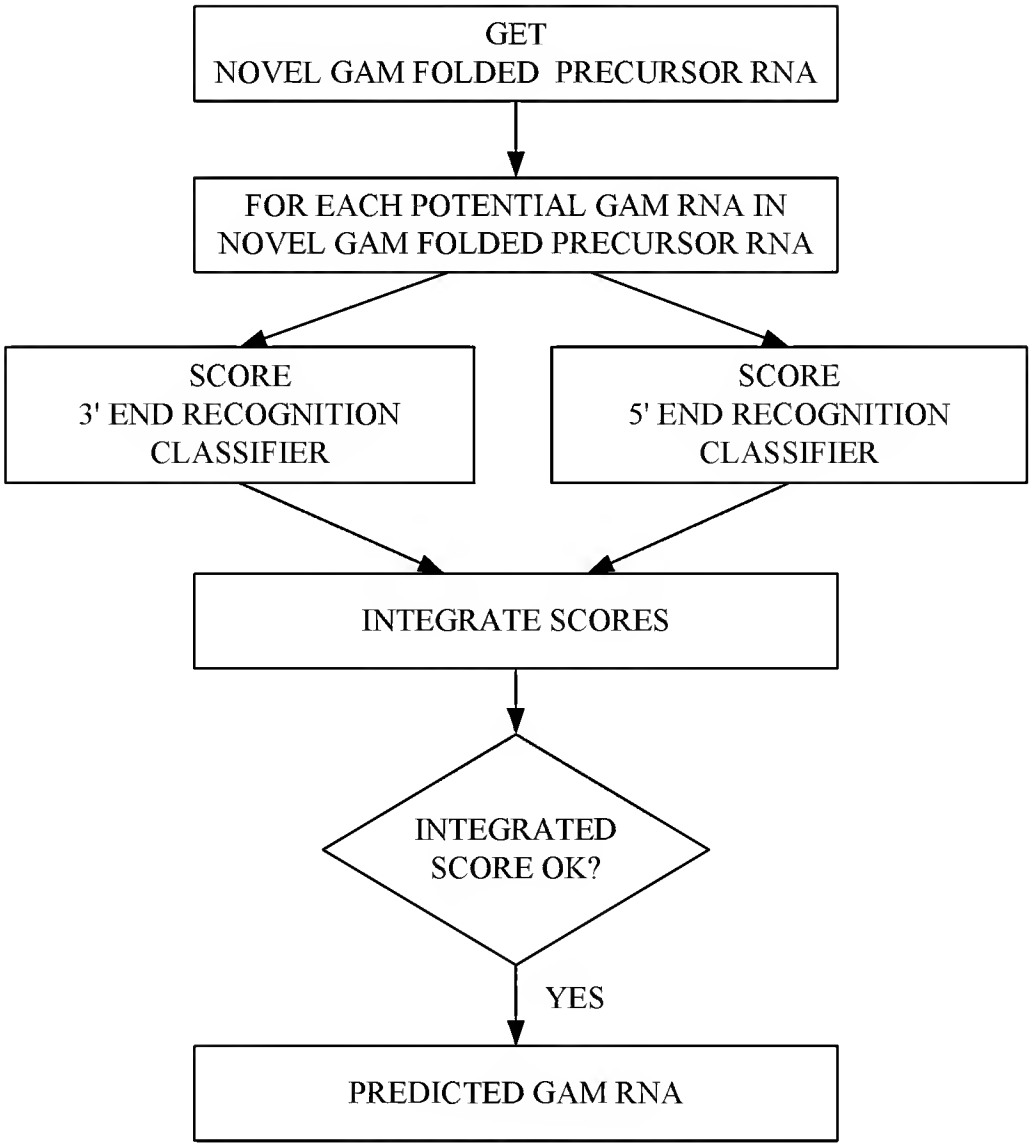

GET
NOVEL GAM FOLDED PRECURSOR RNA
FOR EACH POTENTIAL GAM RNA IN
NOVEL GAM FOLDED PRECURSOR RNA
SCORE
3' END RECOGNITION
CLASSIFIER
SCORE
5' END RECOGNITION
CLASSIFIER
INTEGRATE SCORES
INTEGRATED
SCORE OK?
YES
PREDICTED GAM RNA

FIG. 14A

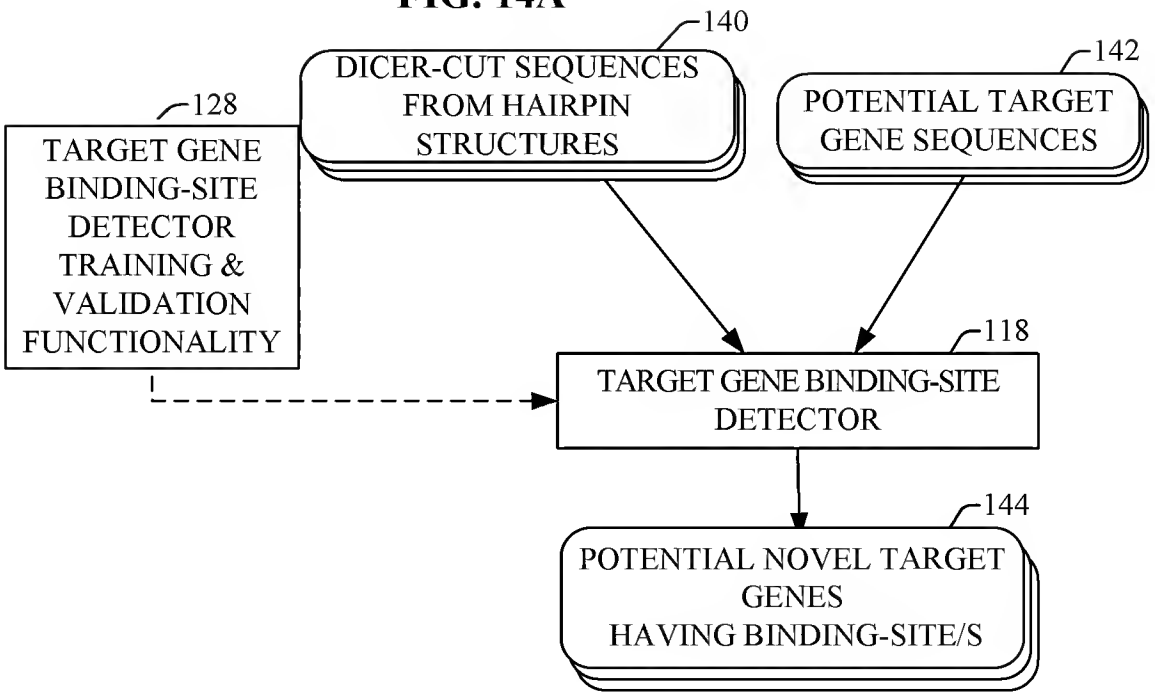


FIG. 14B

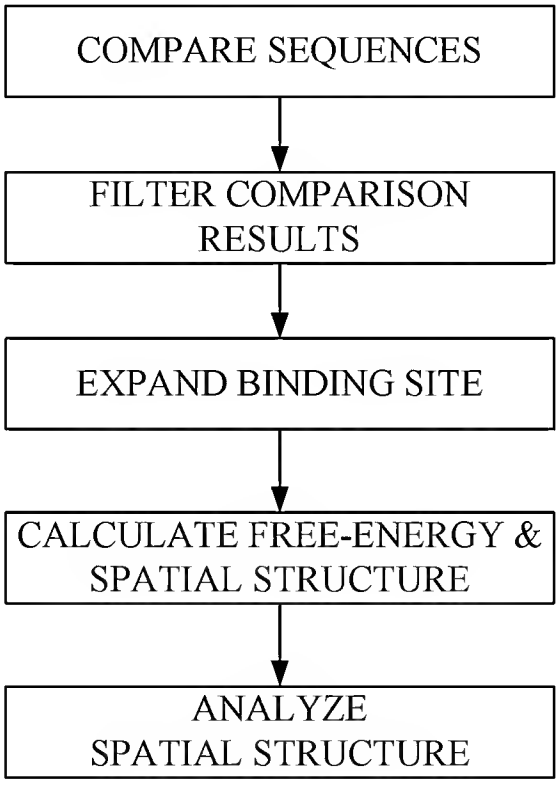


FIG. 15

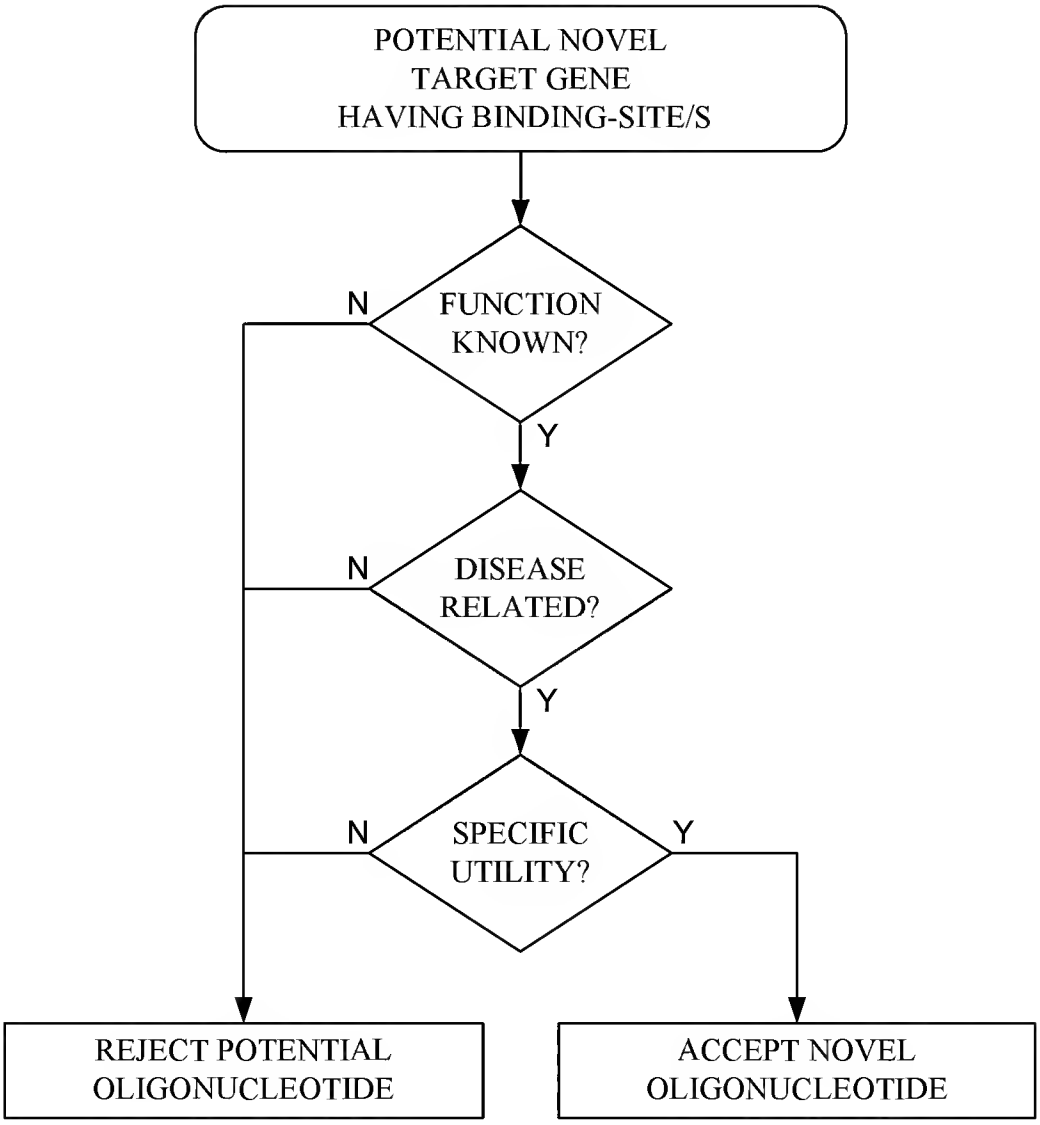

POTENTIAL NOVEL
TARGET GENE
HAVING BINDING-SITE/S
FUNCTION
KNOWN?
N
Y
DISEASE
RELATED?
N
Y
SPECIFIC
UTILITY?
N
Y
REJECT POTENTIAL
OLIGONUCLEOTIDE
ACCEPT NOVEL
OLIGONUCLEOTIDE

FIG. 16

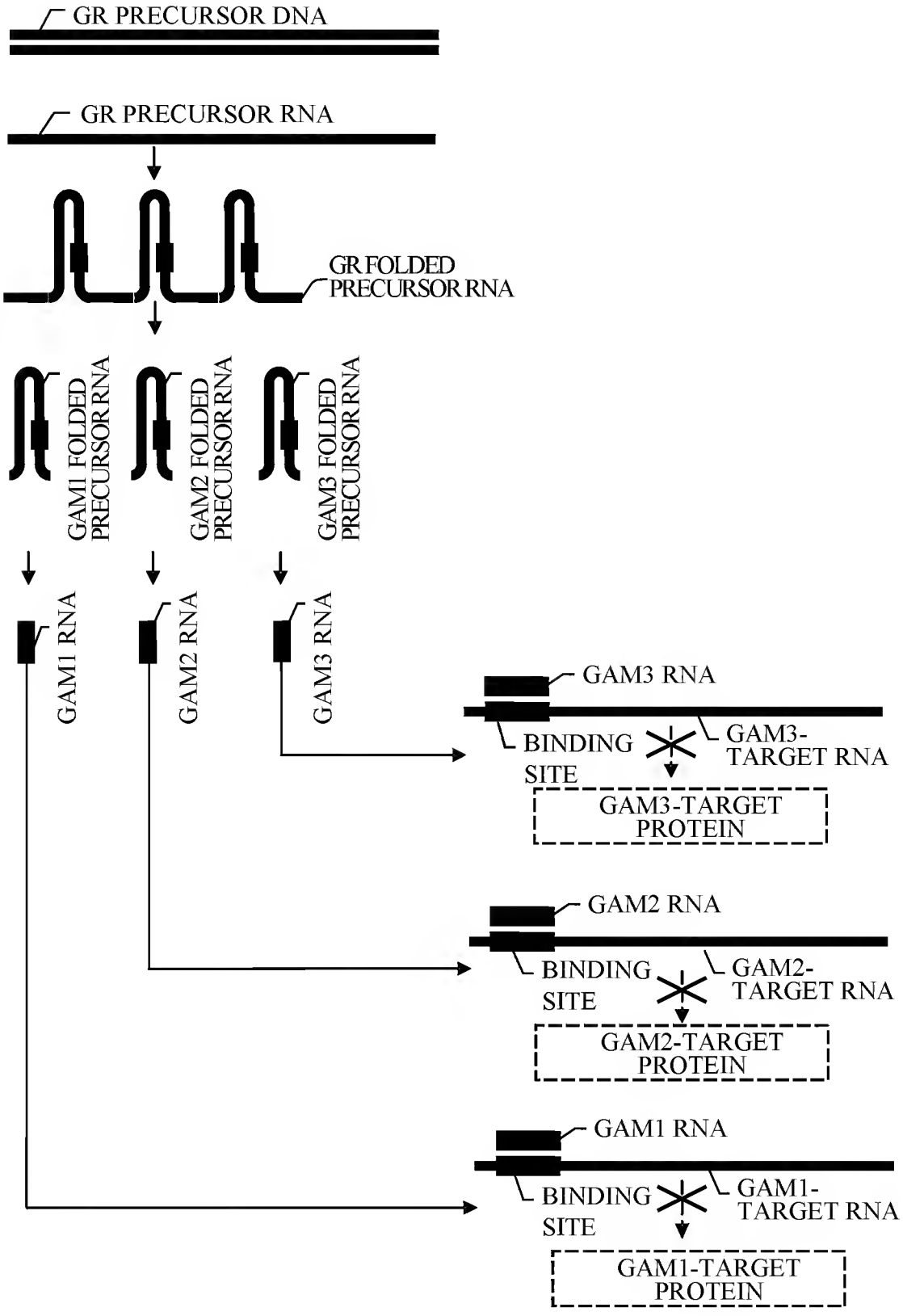

GR PRECURSOR DNA
GR PRECURSOR RNA
GR FOLDED PRECURSOR RNA
GAM1 FOLDED PRECURSOR RNA
GAM2 FOLDED PRECURSOR RNA
GAM3 FOLDED PRECURSOR RNA
GAM1 RNA
GAM2 RNA
GAM3 RNA
GAM3 RNA
BINDING SITE
GAM3-TARGET RNA
GAM3-TARGET PROTEIN
GAM2 RNA
BINDING SITE
GAM2-TARGET RNA
GAM2-TARGET PROTEIN
GAM1 RNA
BINDING SITE
GAM1-TARGET RNA
GAM1-TARGET PROTEIN

FIG. 17

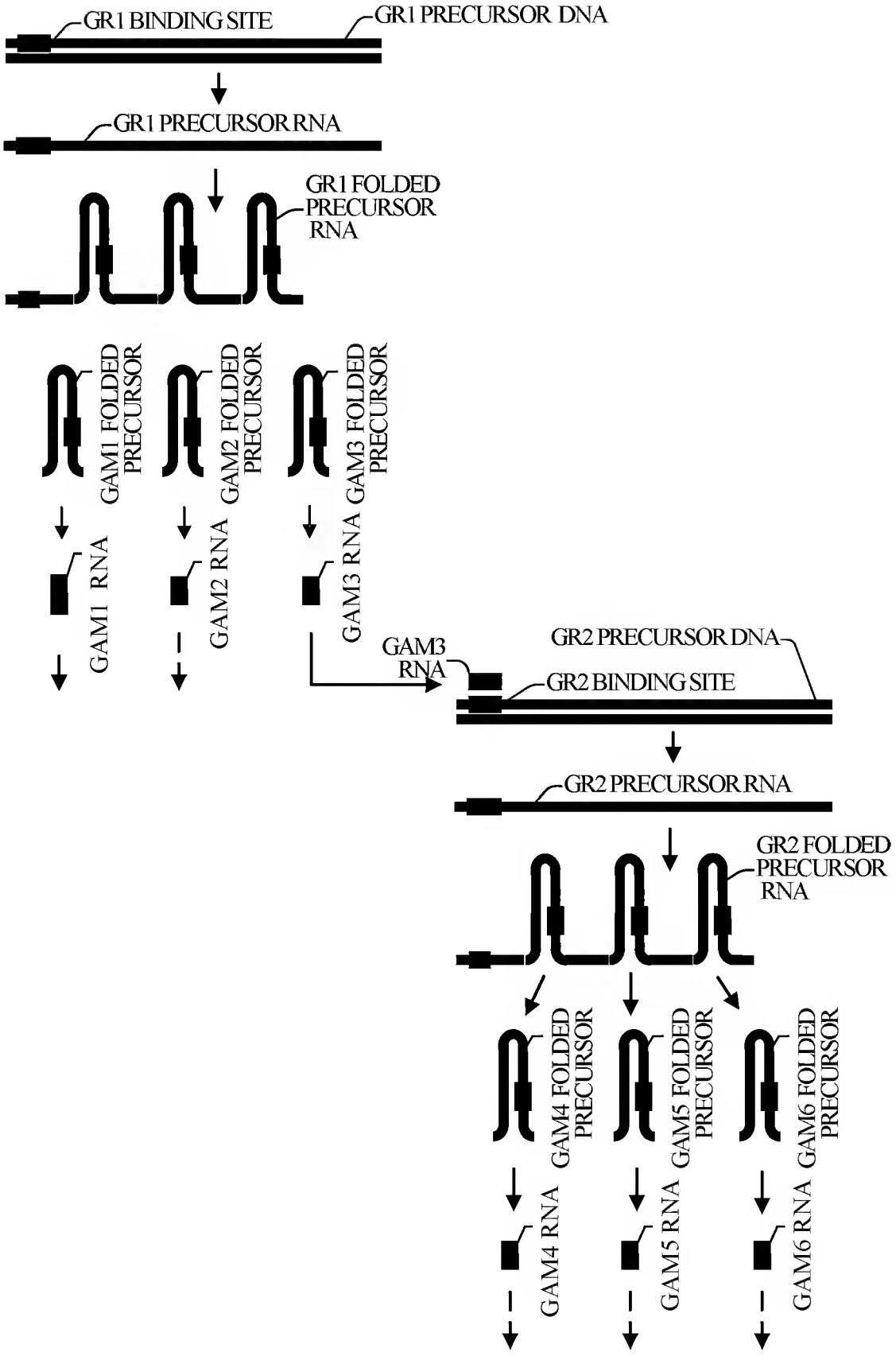

GR1 BINDING SITE
GR1 PRECURSOR DNA
GR1 PRECURSOR RNA
GR1 FOLDED PRECURSOR RNA
GAM1 FOLDED PRECURSOR
GAM2 FOLDED PRECURSOR
GAM3 FOLDED PRECURSOR
GAM1 RNA
GAM2 RNA
GAM3 RNA
GAM3 RNA
GR2 PRECURSOR DNA
GR2 BINDING SITE
GR2 PRECURSOR RNA
GR2 FOLDED PRECURSOR RNA
GAM4 FOLDED PRECURSOR
GAM5 FOLDED PRECURSOR
GAM6 FOLDED PRECURSOR
GAM4 RNA
GAM5 RNA
GAM6 RNA

FIG. 18

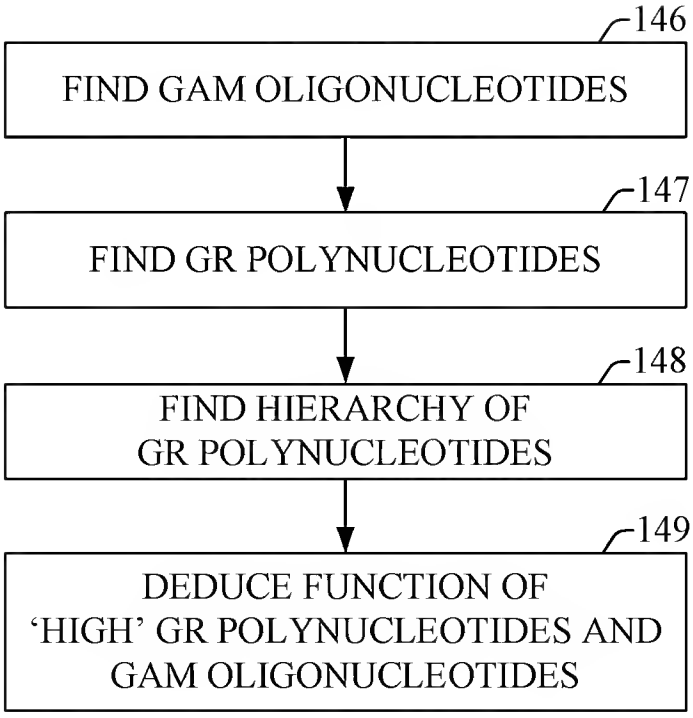

146
FIND GAM OLIGONUCLEOTIDES
147
FIND GR POLYNUCLEOTIDES
148
FIND HIERARCHY OF
GR POLYNUCLEOTIDES
149
DEDUCE FUNCTION OF
'HIGH' GR POLYNUCLEOTIDES AND
GAM OLIGONUCLEOTIDES

FIG. 19

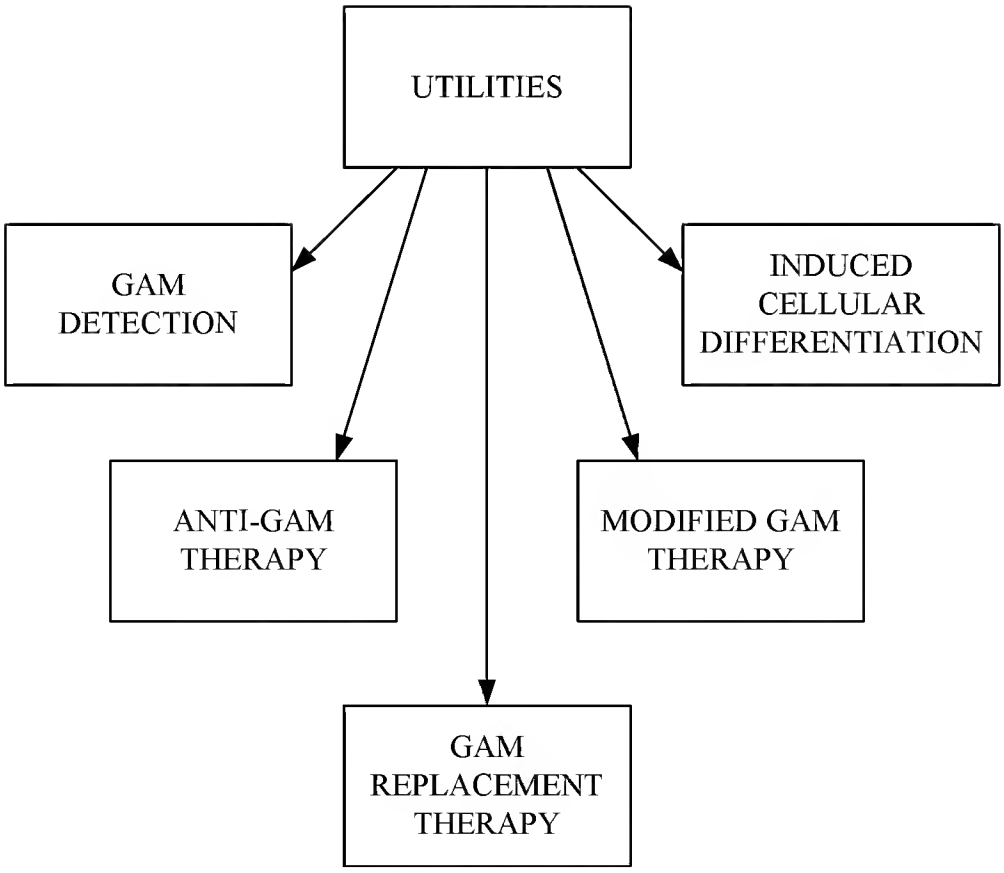

UTILITIES
GAM DETECTION
INDUCED CELLULAR DIFFERENTIATION
ANTI-GAM THERAPY
MODIFIED GAM THERAPY
GAM REPLACEMENT THERAPY

FIG. 20A

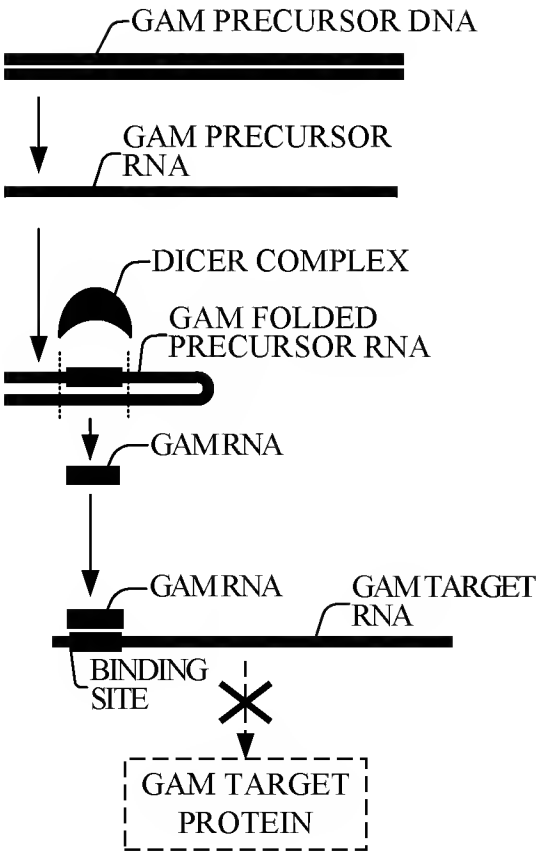


FIG. 20B

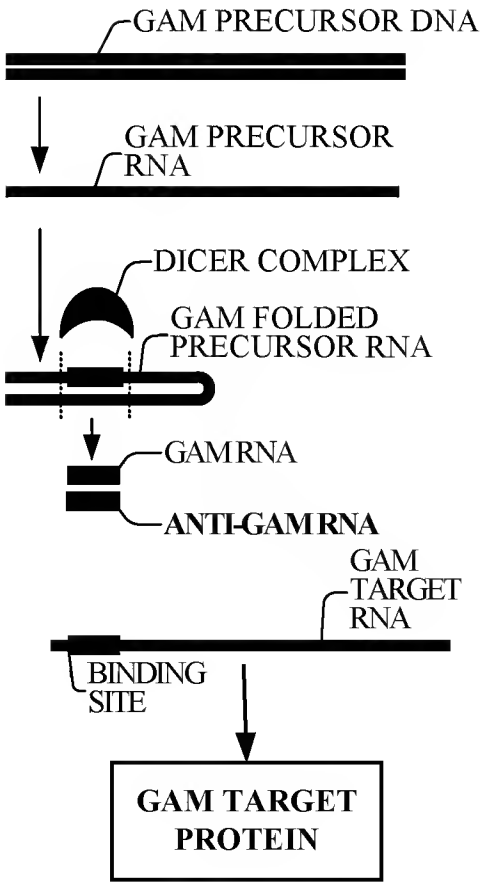


FIG.21A

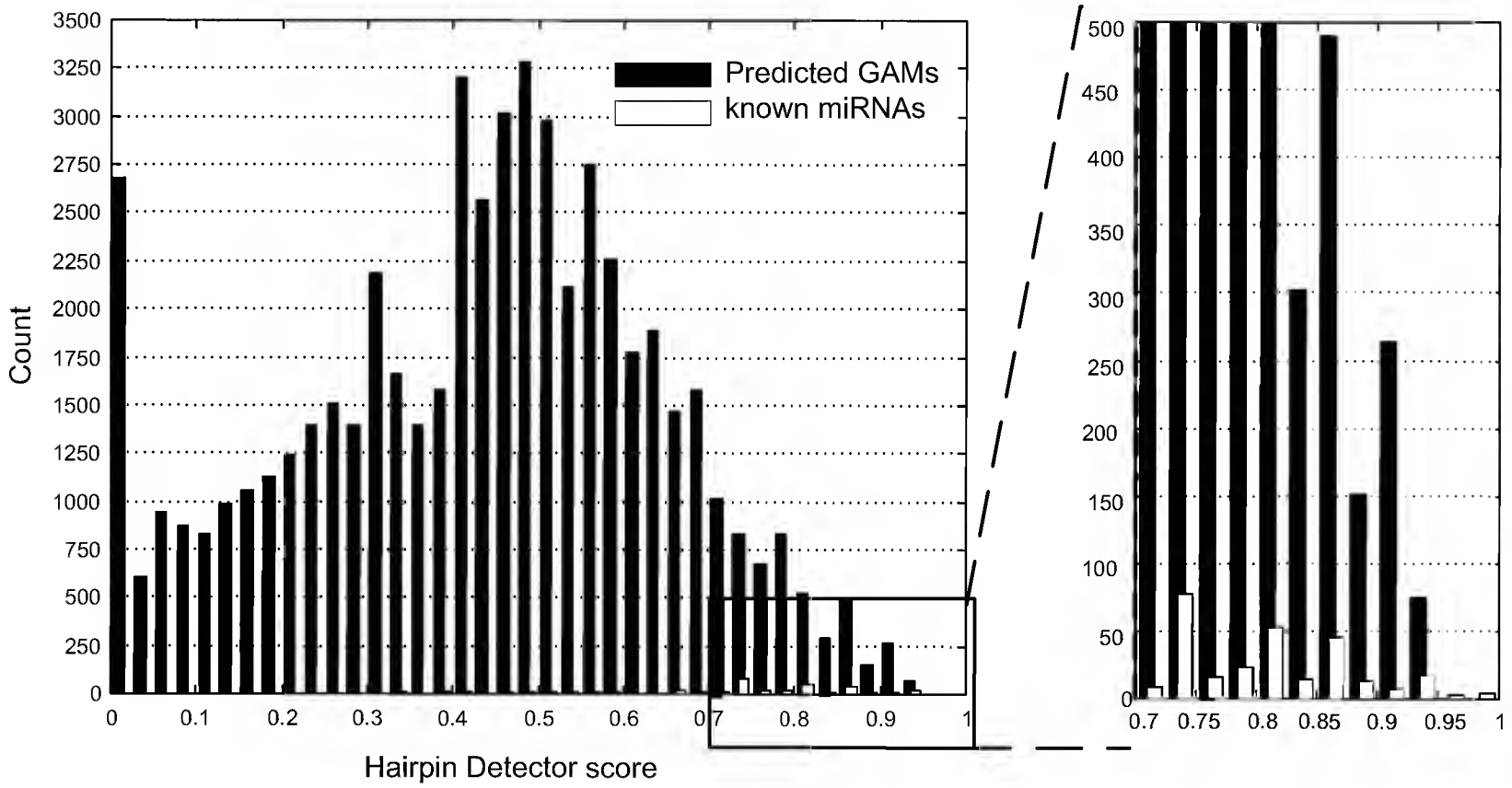

Predicted GAMs
known miRNAs
Count
Hairpin Detector score
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
250
0
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
500
450
400
350
300
250
200
150
100
50
0
0.7
0.75
0.8
0.85
0.9
0.95
1

FIG. 21B

GAM Detection Accuracy Group	Number of published hairpins	Precision on hairpin mixture	Lab validation of Human GAMs			Hairpins in RNA databases	Hairpins of the present invention
			Sent	Positive	% success		
A	228	76%	101	37	37%	2821	1419
B	135	41%	56	13	23%	19950	333
C	27	18%	7	1	14%	11765	18
D	20	10%	4	1	25%	7876	2
Overall	410	44%	168	52	31%	42416	1708

FIG. 22A

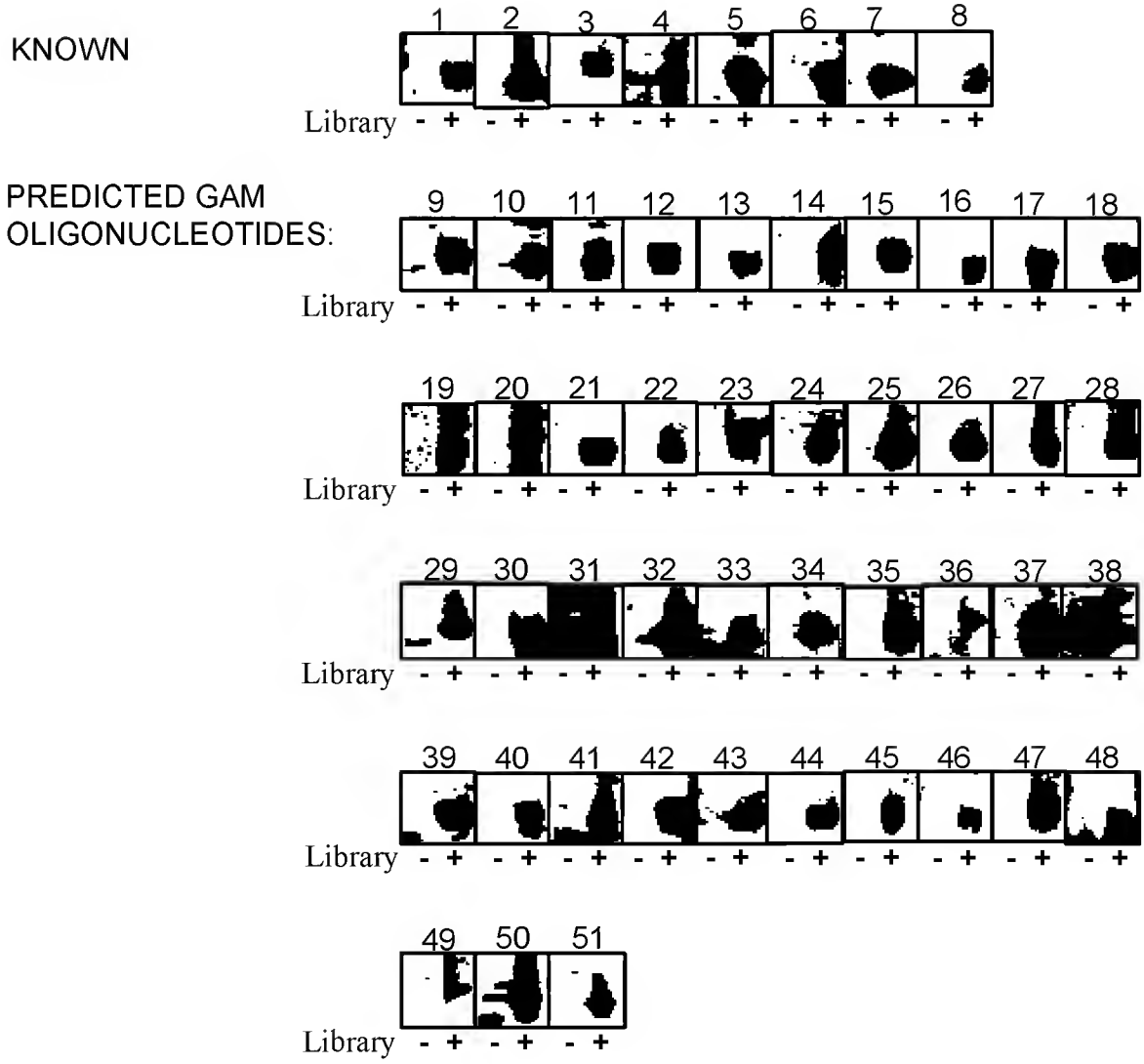

KNOWN
1 2 3 4 5 6 7 8
Library - + - + - + - + - + - + - + - +
PREDICTED GAM OLIGONUCLEOTIDES:
9 10 11 12 13 14 15 16 17 18
Library - + - + - + - + - + - + - + - + - + - +
19 20 21 22 23 24 25 26 27 28
Library - + - + - + - + - + - + - + - + - + - +
29 30 31 32 33 34 35 36 37 38
Library - + - + - + - + - + - + - + - + - + - +
39 40 41 42 43 44 45 46 47 48
Library - + - + - + - + - + - + - + - + - + - +
49 50 51
Library - + - + - +

FIG. 22B

NUMBER	NAME	SEQUENCE (5 TO 3)	SEQUENCED
1	hsa-miR-21	TAGCTTATCAGACTGATGTTGA	+
2	hsa-miR-27b	TTCACAGTGGCTAAGTTCTGCA	+
3	hsa-miR-186	AAAGAATTCTCCTTTTGGGCTT	+
4	hsa-miR-93	AAGTGCTGTTCGTGCAGGTAGT	+
5	hsa-miR-26a	TCAAGTAATCCAGGATAGGCTG	+
6	hsa-miR-191	AACGGAATCCCAAAAGCAGCTG	+
7	hsa-miR-31	GGCAAGATGCTGGCATAGCTGT	+
8	hsa-miR-92	TATTGCACTTGTCCCGGCCTGT	+
9	GAM3418-A	ATCACATTGCCAGGGATTACCA	+
10	GAM4426-A	GAAGTTTGAAGCCTGTTGTTCA	+
11	GAM281-A	CACTGCACTCCAGCCTGGGCAA	
12	GAM7553-A	TAGGTAGTTTCCTGTTGTTGGG	+
13	GAM5385-A	TCACAGTGAACCGGTCTCTTTC	+
14	GAM2608-A	TAAGGTGCATCTAGTGCAGTTA	
15	GAM1032-A	CTAGACTGAAGCTCCTTGAGGA	+
16	GAM3431-A	TAATACTGCCGGGTAATGATGG	
17	GAM7933-A	TAGCAGCACATAATGGTTTGAA	
18	GAM3298-A	AAAGTGCTCATAGTGCAGGTAG	+
19	GAM7080-A	TTTCCACAGCGGCCAATTCTTC	+
20	GAM895-A	AGCTGCCAGTTGAAGAACATTT	
21	GAM3770-A	AAGTTAAGAGCTCCCAGGCCTG	
22	GAM337162-A	ACTGCACTCCAGCCTGGGCAAC	+
23	GAM8678-A	GTGTTCCAGGAAGTCGTCTTGA	
24	GAM2033-A	TCAAGCTCATTCCTCTAACCTC	
25	GAM7776-A	CATTGCACTCCAGCCTGGGCAA	+
26	GAM8145-A	ACATGATCTCCTCACTCTAGGA	
27	GAM25-A	AATTGCTTGAACCCAGGAAGTG	+
28	GAM7352-A	TGTTTAAGTAGCTTATTTATCT	
29	GAM337624-A	TCTAAGAGAAAGGAAGTTCAGA	+
30	GAM1479-A	GAAGGCAGTAGGTTGTATAGTT	+
31	GAM2270-A	ATCACATTGCCAGTGATTACCC	+
32	GAM7591-A	TTGGAGTAATTCAGTATAGGTT	+
33	GAM8285-A	AGTAGACAGTGGCAACATAGTC	
34	GAM6773-A	CTAGCCTGTTTGTCCTCACCCC	+
35	GAM336818-A	TGAGGTGGGATCCCGAGGCC	+
36	GAM336487-A	TGGCTAGGTAAGGGAAG	+
37	GAM337620-A	AATCATCATTATTTTGAAGTTTA	+
38	GAM336809-A	TAAGGCATTTTTATGGT	+
39	GAM5346-A	GCTGTTGTTAAGGGCACTTGGG	
40	GAM8554-A	TTCATGGGAGCAGGTGGTACAG	
41	GAM2701-A	ACTGCACTCCAGTCTGGGTGAC	
42	GAM7957-A	TCACTGCAACCTCTGCCTCCCG	
43	GAM391-A	CAGATCACATCCATCCGTCACC	
44	GAM6633-A	GCACTCAAGCCTGGGTTACAGA	
45	GAM19	AGAGAGTGGCAGGTCTGTTCCT	
46	GAM8358-A	GATGAGGCAGCACTTGGG	
47	GAM3229-A	TGAGGTGGGAGAATTGCTTGAA	
48	GAM7052-A	CATGTAATCCCAGCTACTCAGG	
49	GAM3027-A (mmu-MIR-29c)	TAGCACCATTTGAAATCGGTTA	+
50	GAM21 (mmu -MIR-130b)	CAGTGCAATGATGAAAGGGCAT	+
51	GAM oligonucleotide(mmu-MIR-30e)	TGTAAACATCCTTGACTGGAAG	+

FIG. 23A

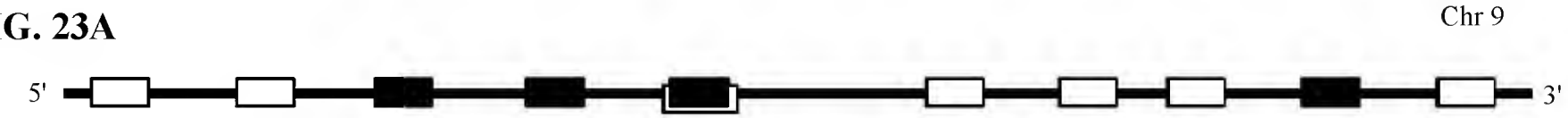


FIG. 23B

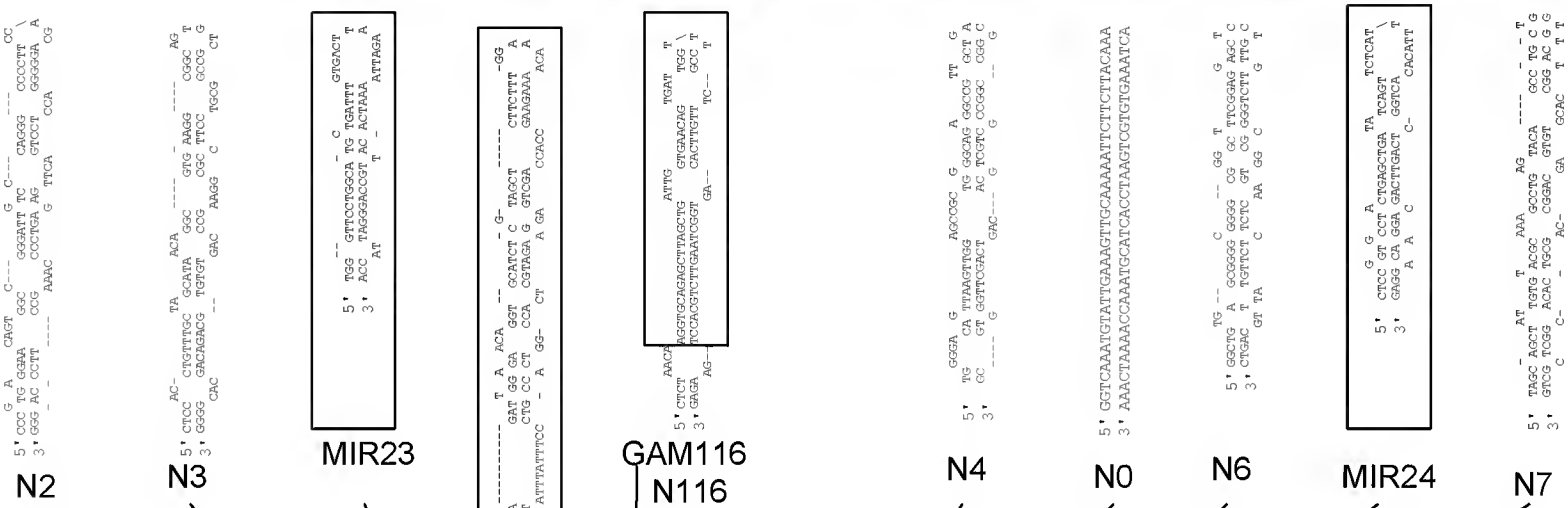


FIG. 23C

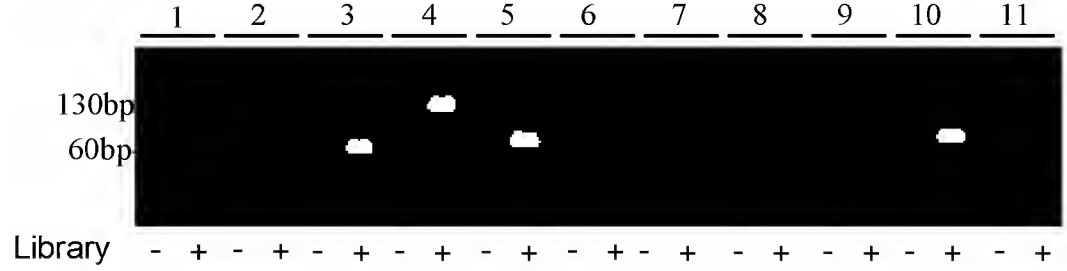


FIG. 24A

EST72223 (705 nt.)

EST72223 sequence:

CCCTTATTAGAGGATTCTGCTCATGCCAGG**GTGAGGTAGTAAGTTGTATTG**
TTGTGGGGTAGGGATATTAGGCCCCAATTAGAAGATAACTATACAACT **MIR98**
TACTACTTTCCCTGGTGTGTGGCATATTCACACTTAGTCTTAGCAGTGTTGCC
TCCATCAGACAAAGTTGTAGATGTTCCTTGGATAATTTGGACTGGAAGAAAAGA
GACATGGAAGGGGACAGATGGTGTTTAGGGTGAGGCAGATGTCATTATAAAGT
GACTTGTCTTTCATTAATTGGAGCATATAATTATTTTACCTTTGGGCATGAACTC
ATTTTGCTATTCTTCAACTGTGTAATGATTGCATTTTATTAGTAATAGAACAGGA
ATGTGTGCAAGGGAATGGAAAGCATACTTTAAGAATTTTGGGCCAGGCGCGGT
GGTTCATGCCTGTAATCCCAGCATTTTTGGGAGGCCGAGGCGGGTGGATCAC
CTGAGGTCAGGAGTTCGAGACCAACCTGGCCAACACGGCGAAACCCCGCCTC
TACTCAAATACAAAAATTAGCCAGGCTTGGTGACACTCGCCTGTGGTCCCAGC
TACTCAGGAGGCT**GAGGCAGGAG**AATTGCTTGAACCCAGGAAGTGGAG **GAM25**
GCTTCAGTGAGCTGAGAACACGCCACTGCACTCCAGTCCTGGGCAAC
AGAGCAAGACTCTGTCTCAGGAAAAAAAAAG

FIG. 24B

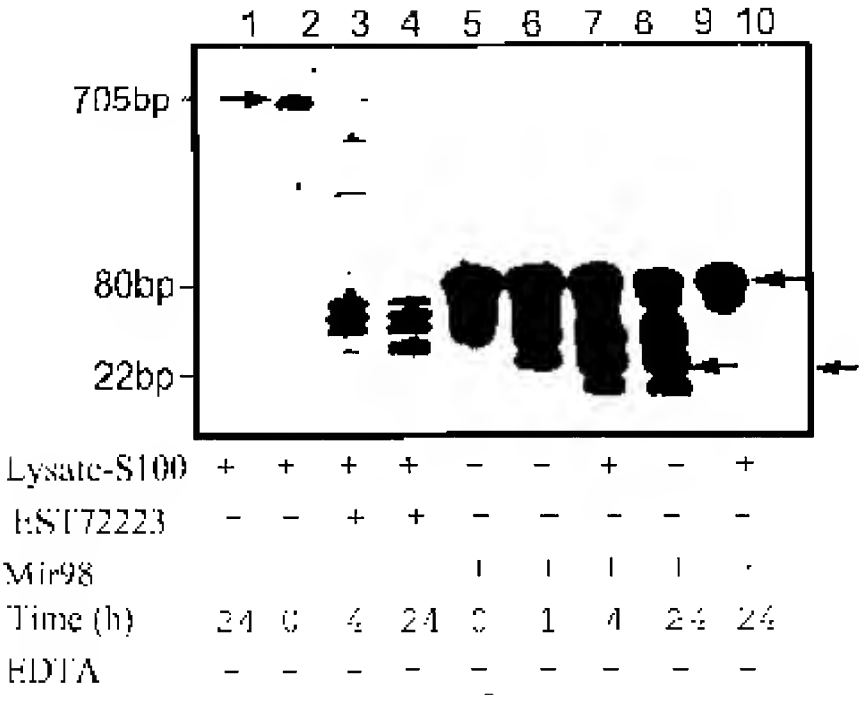
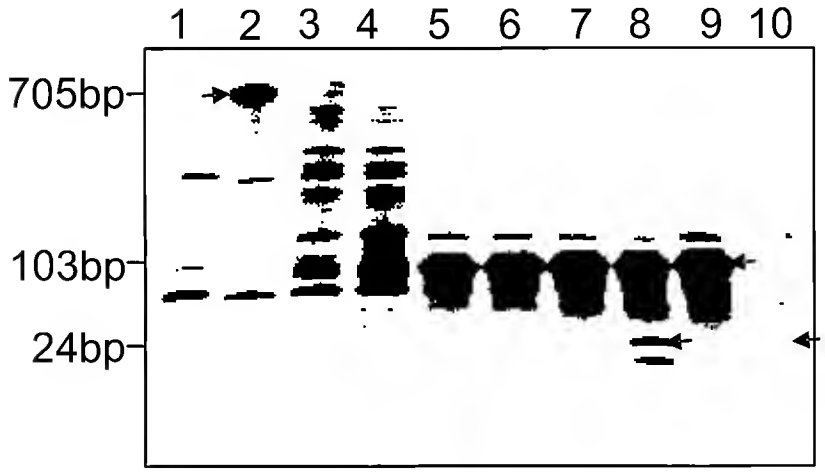
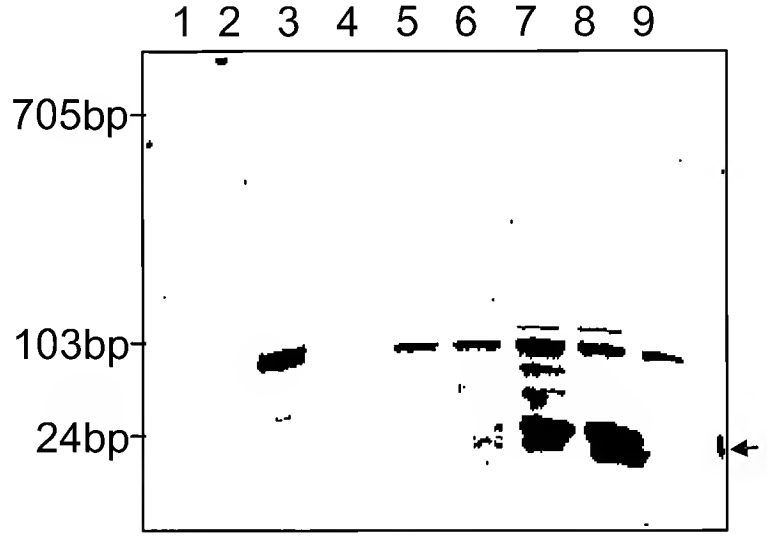


FIG. 24C



Lysate-S100	+	+	+	+	+	+	+	+	+
EST72223	–	+	+	+	–	–	–	–	–
GAM25	–	–	–	–	+	+	+	+	+
Time (h)	24	0	4	24	0	0.5	1	24	24
EDTA	–	–	–	–	–	–	–	–	+

FIG. 24D



Lysate-S100	+	+	+	+	+	+	+	+	+
EST72223	–	+	+	+	–	–	–	–	–
GAM25	–	–	–	–	+	+	+	+	+
Time (h)	24	0	4	24	0	0.5	1	24	24
EDTA	–	–	–	–	–	–	–	–	+